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TOTAL PANCREATECTOMY FOR CARCINOMA OF THE PANCREAS IN A DIABETIC PERSON

Metabolic Studies

CLAUDE F. DIXON, M.D.

MANDRED W. COMFORT, M.D.

A. L. LICHTMAN, M.D.
First Assistant in Surgery, Mayo Clinic
AND
RAYMOND E. BENSON, M.D.
First Assistant in Surgery, Mayo Clinic
ROCHESTER, MINN.

WE ARE presenting a case in which total pancreatectomy was performed for carcinoma of the pancreas developing in a diabetic patient. At the time when this paper was written, twelve months after operation, the patient was living and well. Cases of total pancreatectomy in which the patient is living and well as long as twelve months after operation are sufficiently rare to justify presentation. In fact, we know of only 1 other such case, that of Priestley, Comfort and Radcliffe,[1] in which the patient was living and well eighteen months after operation. Our case is of interest further in that the patient was diabetic before the development of carcinoma and before operation.[2]

Our patient presented an opportunity to make certain observations on the effect of total loss of internal and external pancreatic secretions on metabolic processes. We are presenting data, incomplete as they are, on the formation of ketone bodies during insulin privation, on the loss of foodstuffs in the stool and on hepatic function as a contribution to our knowledge of depancreatized man.

From the Departments of Surgery and Medicine, Mayo Clinic.

1. Priestley, J. T.; Comfort, M. W., and Radcliffe, J., Jr.: Total Pancreatectomy for Hyperinsulinism Due to an Islet-Cell Adenoma: Survival and Cure at Sixteen Months After Operation; Presentation of Metabolic Studies, Ann. Surg. **119**:211-221 (Feb.) 1944.

2. Brunschwig, A.; Ricketts, H. T., and Bigelow, R. R.: Total Pancreatectomy, Total Gastrectomy, Total Duodenectomy, Splenectomy, Left Adrenalectomy and Omentectomy in a Diabetic Patient: Recovery, Surg., Gynec. & Obst. **80**: 252-256 (March) 1945.

REPORT OF A CASE

The patient was a white man, aged 50 years, whose history included attacks of pneumonia, typhoid fever, rheumatic fever and pleurisy. In November 1942, after a period of polyuria, polydipsia, polyphagia and loss of strength, he lost consciousness in diabetic coma and was treated with insulin. His condition improved under a regimen that included 22 units of protamine zinc insulin daily. In July 1943 he began to have chills and fever, with a temperature up to 102 F. This condition was diagnosed as malaria, and he was given a course of quinacrine hydrochloride. Jaundice and pruritus soon were noted, and the patient lost 50 pounds (22.7 Kg.). His course continued to be downhill. He began to have hematemesis, and many transfusions were given. In December 1943, cholecystojejunostomy was performed by his local surgeon. The gallbladder was described as thick and edematous, the common duct was distended and the pancreas was enlarged and edematous. The fasting blood sugar ranged from 114 to 360 mg. per hundred cubic centimeters, and the icterus index varied from 50 to 180. The jaundice and pruritus cleared, and the patient was well until April 1944, when he again began to have massive emesis.

On examination at the Mayo Clinic in May 1944, the patient was acutely ill and dehydrated. Gastric retention exceeded 1,000 cc. Examination of the fluid

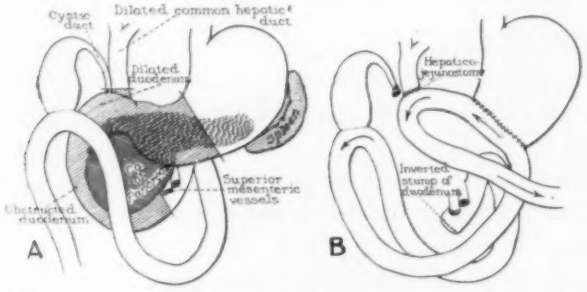

Fig. 1.—*A*, location of carcinoma of the pancreas; tissue to be resected is shaded; the broken lines represent the portion of the pancreas behind the stomach; *B*, arrangement after total pancreatectomy, splenectomy, partial duodenectomy, partial gastrectomy, resection of common duct, gastrojejunostomy and hepaticojejunostomy.

revealed absence of free acid except on one occasion, when 20 units of free hydrochloric acid was found. At this time he was taking 24 units of protamine zinc insulin daily. Roentgenographic examination after ingestion of barium sulfate showed an obstructing lesion of the duodenum in the region of the ampulla of Vater.

After suitable preoperative preparation, celiotomy was performed on May 12, 1944. The details of the surgical findings and procedure were as follows:

Through an upper left rectus muscle–splitting incision, a large tumor of the head and body of the pancreas was identified (fig. 1 *a*). This tumor, which was obscured by edema and the surrounding reaction, was encircling and constricting the second portion of the duodenum. The tail of the pancreas was atrophic and nodular. Since examination of the abdominal viscera failed to reveal metastasis, pancreatectomy was undertaken, after the relatives had been consulted. Removal of the spleen improved the exposure, reduced the bleeding and provided an approach for dissecting the tail and body of the pancreas from its bed. The second portion of the duodenum was reflected medially, with ligation of the gastroduodenal and

the inferior pancreaticoduodenal vessels. Since at this point progress was impeded by the anastomosis made at the time of cholecystenterostomy in 1943, the gallbladder was disconnected from the jejunum. What appeared to be a dilated (2 cm.) common duct was actually the cystic and the hepatic duct, closely fused to the duodenum. The right gastric and gastroepiploic vessels were ligated, and

Fig. 2.—Resected portion of the stomach and duodenum and the entire pancreas; *a*, anterior view and, *b*, posterior view.

the distal third of the stomach was freed. Dissection over the portal vein and the superior mesenteric vessels was difficult and hazardous. The stomach was transected, and the duodenum was divided short of the ligament of Treitz. The

pancreas, duodenum and distal third of the stomach were removed (fig. 1 *A*). The duodenal stump was inverted close to the transverse mesocolon. Anterior gastrojejunostomy (end to side) was performed, and distal to the stoma the dilated hepatic duct was implanted into the jejunum at a convenient site (fig. 1 *B*). The extent of the resection permitted careful verification of total removal of the pancreas. After intraperitoneal distribution of 5 Gm. of sulfathiazole, the abdomen was closed. Despite the length of the procedure (three hours and forty minutes), the pulse rate never was more than 100 beats per minute. Whole blood, 2,500 cc., was given intravenously during and after the procedure as a supportive measure.

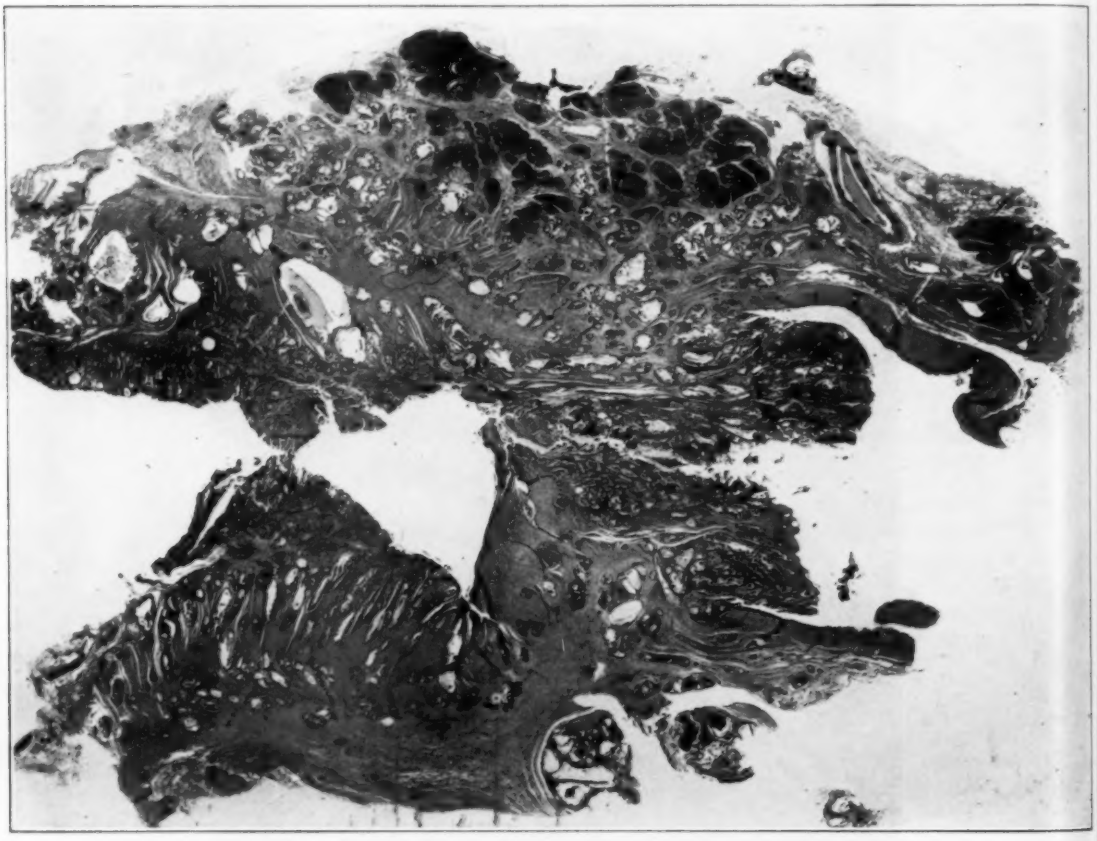

Fig. 3.—Carcinoma of the pancreas (× 2).

The pathologists reported that the specimen consisted of 10 cm. of stomach, 15 cm. of duodenum and the entire pancreas (fig. 2). A normal spleen also was included. The tumor in the head of the pancreas was an ulcerative mucous adenocarcinoma, grade 2 (Broders' classification), that had compressed and ulcerated the duodenum (fig. 3). The common duct was short, dilated and completely obstructed. The stumps of the cystic and hepatic ducts were dilated. Many peripancreatic nodes revealed lymphatic involvement. The stomach was greatly dilated but was otherwise normal.

The postoperative course was surprisingly uneventful, and the patient swung his feet out of bed on the eighth postoperative day. The highest recorded temperature was 101.4 F. On the forty-fifth postoperative day, after a spell of vomiting, roentgenologic examination revealed a normally functioning gastrojejunal stoma. The amount of insulin administered during the first thirty-five days is given in table 1. From the twenty-second to the seventy-ninth postoperative day and from the two hundred and thirtieth to the two hundred and fifty-first day, detailed metabolic studies were made. The patient was ambulatory during all of this time. His cooperation was wholehearted, since he previously had been told that nothing could be done for him. Between the time of his dismissal, on the seventy-ninth postoperative day, and his return, seven months after operation, for review of his condition, he had regained his strength and had gone back to work. He had taken 24 enteric-coated pancreatin tablets daily and had had one large formed stool daily. His insulin requirement was filled by the administration of 40 units of protamine zinc insulin daily. Twelve months after operation the patient reported that his condition was good.

TABLE 1.—*Insulin Administered After Total Pancreatectomy*

Days After Operation	Units of Regular Insulin Required Daily
1	20
2	52
3	52
4	20
5	52
6	40
7	44
8 to 14	20 to 40
15 to 21	30
22 to 28	16 to 36
29 to 35	32 to 36

EFFECT OF INSULIN PRIVATION ON A TOTALLY DEPANCREATIZED HUMAN BEING

An effort was made to study some of the changes in the patient's metabolism during insulin privation. Insulin was withheld during two intervals, each of eighty-nine hours' duration, in order to determine the relative tendency toward the development of ketosis. The diet from the fifty-first to the seventy-ninth day, which included the first interval of insulin privation, contained 2,940 calories, 440 Gm. of carbohydrates, 100 Gm. of protein and 100 Gm. of fat, together with 45 pancreatin tablets daily. On the sixty-second day the use of ordinary insulin in doses of 30 units morning and evening was begun; the last dose was given at 6 p. m. on the sixty-sixth day. The administration of insulin was resumed eighty-nine hours later, thus providing a basal period before deprivation and a period of adjustment afterward.

Qualitative determinations of urinary sugar, acetone and diacetic acid were performed four times a day. Determinations of the blood

sugar, chlorides and urea were performed daily before and after insulin privation. While the patient was deprived of insulin, determinations were made three times a day to check on any abrupt change that might occur. Occasional determinations of calcium, phosphorus, cholesterol, cholesterol esters, lecithin, fatty acids, total lipids and protein with albumin-globulin ratio were performed. The respiratory quotient and corrected basal metabolic rate were recorded daily.

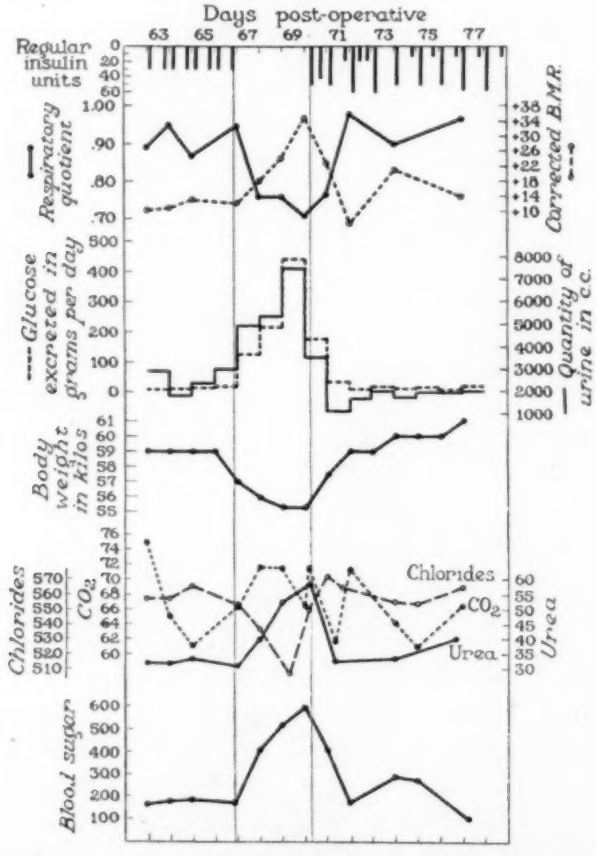

Fig. 4.—Laboratory data before, during and after first interval of insulin privation, which is indicated by the two vertical lines.

Results of some of the determinations before, during and after the first interval, of eighty-nine hours, of lack of insulin are given in figure 4. During the basal period with insulin, the respiratory quotient ranged from 0.87 to 0.95. At the end of the period of privation it was 0.71. At this time the corrected basal metabolic rate was +37 per cent. During the last twenty-four hours of the time the patient was without insulin, he excreted 423.16 Gm. of glucose in 7,450

cc. of urine. He lost 3.1 Kg. in the eighty-nine hour period. The fasting blood sugar before insulin privation ranged from 158 to 179 mg. per hundred cubic centimeters; during the period without insulin it rose to 402 to 594 mg. After ingestion of about 100 Gm. of dextrose in the fifty-fifth hour of insulin deprivation, the blood sugar rose to 813 mg. At this time the patient complained of dizziness and weakness. Determination of the carbon dioxide–combining power did not show any evidence of acidosis; the value was 65.5 volumes per hundred cubic centimeters of plasma in the eighty-ninth hour. The chloride value fell to 507 mg. per hundred cubic centimeters of plasma. With the low concentration of chloride, the patient complained of severe abdominal and muscular cramps. These were relieved dramatically by the administration of 3 Gm. of sodium chloride by mouth. The urea rose to 57 mg. per hundred cubic centimeters of blood, despite the excretion of a tremendous quantity of urine. Determinations of urinary acetone and diacetic acid gave negative results except during the last eight hours of insulin deprivation, when a faint trace of acetone was found. This faint trace persisted for twenty-four hours after administration of insulin was started, even though the qualitative sugar determination was as low as 1 plus, with 33.5 Gm. of glucose excreted in twenty-four hours. During the last twenty-four hours of insulin privation, the total nitrogen excreted in the urine was 18.8 Gm. During the period with insulin, the total excretion of nitrogen was 11.3 Gm.

After intensive study, the patient was dismissed in good condition on the seventy-ninth postoperative day. During sixty-five of the seventy-nine days, he assumed normal activity. His weight was greater than it had been previous to operation.

On the two hundred and thirtieth postoperative day, the patient returned to the clinic for further metabolic studies. It will be recalled that during the first interval he had received 440 Gm. of carbohydrate daily. In order to make a more critical test of the tendency toward development of ketosis after pancreatectomy, 120 Gm. of carbohydrate, 100 Gm. of protein and 135 Gm. of fat were given for four days previous to and during the second interval of insulin privation. On the second day of the second interval of privation, the patient excreted as much as 164 Gm. of glucose. The resulting depletion of hepatic glycogen would provide conditions more favorable for the development of ketosis than existed in the first interval of privation. Furthermore, an attempt was made in the second interval to compensate for the great loss of salt by oral administration of 750 cc. of a salt mixture daily. This provided 7.5 Gm. of sodium chloride and 3.75 Gm. of sodium citrate daily before, during and after privation. It was hoped

that this would diminish the severe weakness and abdominal cramps, which were the only complaints of the patient during the first interval.

Determinations were made of the daily urinary excretion of glucose, total nitrogen, betahydroxybutyric acid, chlorides, sodium and potassium. Specimens of blood were analyzed daily for carbon dioxide content, betahydroxybutyric acid, sodium, potassium and glucose. Hematocrit readings did not show significant changes, roughly ruling out mass shifts due to hemoconcentration. Except for these alterations, that is, reduction of carbohydrate intake, addition of salt solution and

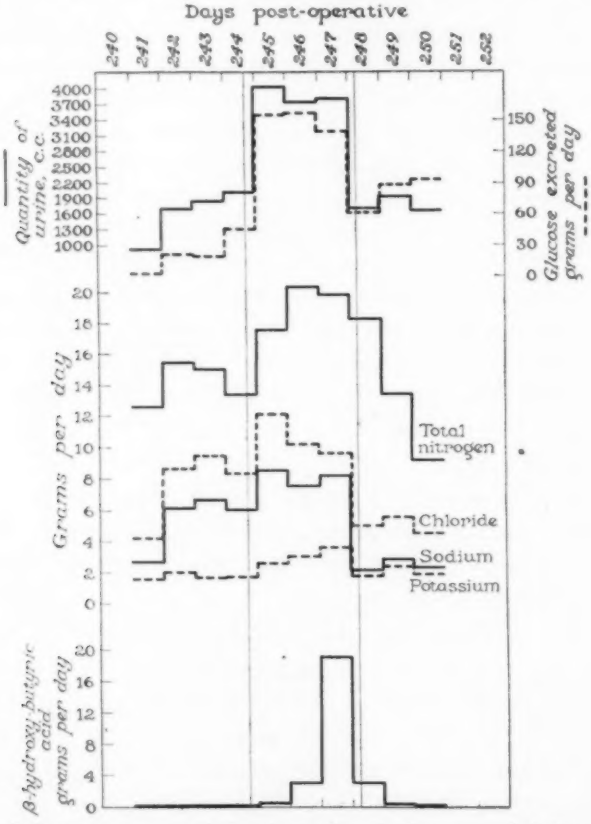

Fig. 5.—Substances excreted in the urine during second interval of insulin privation (indicated by two vertical lines).

more extensive urinary and blood determinations, the second interval of deprivation of insulin was similar to the first. In both intervals, insulin was withheld for eighty-nine hours.

The results of the various studies in the second interval are shown in figures 5 and 6. The patient lost 3.6 Kg. of body weight. On the last day of privation, loss of appetite limited his intake to 1,374 calories (82 Gm. of carbohydrate). His maximal water intake, which occurred

on the second day of insulin privation, was 5,100 cc. For the three days, the urine showed a 4 plus reduction. During the last twenty-four hours the result of the test for acetone and diacetic acid in the urine was 1 plus; this amounted quantitatively to a urinary excretion of 19.1 Gm. (184 milliequivalents) of betahydroxybutyric acid. During these twenty-four hours, the concentration of betahydroxybutyric acid in the blood rose from 4.64 milliequivalents per liter of plasma to 10.2 milliequivalents. Diuresis was accompanied with increased excretion of nitrogen, potassium, chlorides and sodium. The plasma sodium

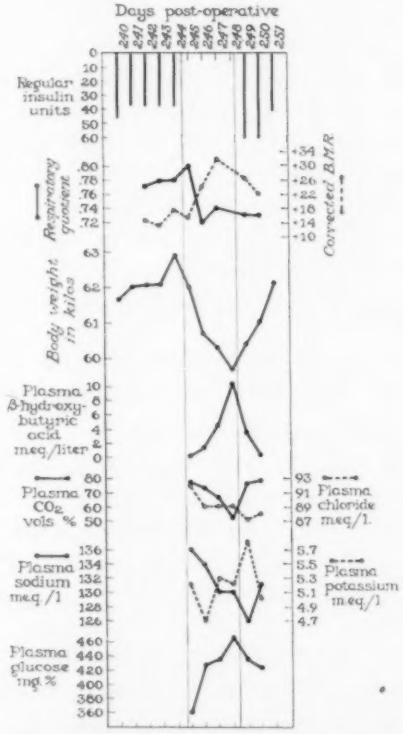
Days post-operative
240 241 242 243 244 245 246 247 248 249 250 251
Regular insulin units
0 10 20 30 40 50 60
Respiratory quotient
.80 .78 .76 .74 .72
Corrected B.M.R.
+34 +30 +26 +22 +18 +14 +10
Body weight in kilos
63 62 61 60
Plasma β-hydroxy-butyric acid mg./liter
10 8 6 4 2 0
Plasma CO2 vols %
80 70 60 50
Plasma chloride
93 91 89 87 m.eq./l.
Plasma sodium m.eq./l
136 134 132 130 128 126
Plasma potassium m.eq./l
5.7 5.5 5.3 5.1 4.9 4.7
Plasma glucose mg.%
460 440 420 400 380 360

Fig. 6.—Insulin dosage, basal metabolic rate, respiratory quotient, weight and blood chemistry during second interval of insulin privation (indicated by two vertical lines).

fell to 126 milliequivalents per liter, and the potassium rose to 5.8 milliequivalents. In the first interval, appreciable ketosis was lacking and the carbon dioxide did not fall significantly; in the second interval, during the last few hours of insulin privation there was a small reduction of the carbon dioxide content to 52 volumes per hundred cubic centimeters of plasma.

The patient remained ambulatory during the second period of privation except during the last few hours. He complained of severe

diaphoresis during the second interval, whereas this did not occur during the first interval. Perspiration was pronounced, but this loss of body fluid was not measured. This prevented any attempt at balance studies. The patient observed another difference between the two intervals. In the first interval, diuresis was greater than in the second interval and was distributed equally through the day and night. On the other hand, in the second interval polyuria was greater at night than during the day, with an excretion of less than 1,500 cc. in the daylight hours. In interpreting this, one should remember that in the daytime the patient was exercising, eating at four to six hour intervals and taking the salt mixture.

The respiratory quotients differed somewhat from those of the first interval in that the range on the preliminary basal run with insulin was 0.77 to 0.8 as compared with 0.87 to 0.95 in the first interval. This may have been the result of the lower carbohydrate intake of the second period. After the privation of insulin, quotients between 0.72 and 0.74 were obtained, which compare favorably with those of depancreatized animals. Much discussion without conclusions was provoked by the reciprocal relationship of the corrected basal metabolic rates and the respiratory quotients as noted in both intervals.

EFFECT OF TOTAL LACK OF EXTERNAL PANCREATIC SECRETION ON DIGESTION AND ABSORPTION

On the twenty-first postoperative day, the patient was ambulatory and in good general condition. He was eating an adequate diet, and the diabetes was under control. His weight was 56.7 Kg., and his basal caloric utilization was 1,680 calories as computed by the Boothby nomogram. His diet contained a daily average of 271.4 Gm. of carbohydrate, 120.6 Gm. of protein (19.3 Gm. of nitrogen), 100.5 Gm. of fat, 2.5 Gm. of calcium and 2.3 Gm. of phosphorus. The value for carbohydrate was estimated according to Sherman's tables; those for protein, fat, phosphorus and calcium were obtained by chemical analysis. These equaled 2,472.5 calories or approximately basal plus 50 per cent. After a preliminary period on this diet, the stools and the urine were collected during three periods of study. Period I (twelve days) included the twenty-fifth to thirty-sixth postoperative days inclusive, period II (six days) the thirty-seventh to forty-second postoperative days and period III (six days) the two hundred and thirty-second to two hundred and thirty-seventh postoperative days inclusive. The intake of food was isocaloric throughout the three periods. The program followed during period II differed from that of periods I and III in only one respect. During period II, 15 enteric-coated tablets of concentrated pancreatin (Wilson Laboratories) were given with each meal, a total of 45 tablets, or 15 Gm., a day. This increased

the average daily nitrogen intake from 19.3 to 20.98 Gm. and of calcium from 2.5 to 4.64 Gm. The diabetes was well controlled with insulin throughout the periods of observation.

Another period of observation of six days, while the patient was taking pancreatin, was started but was interrupted by the development of abdominal pain and vomiting on the forty-fifth postoperative day. Subsequent investigation did not disclose obstruction of the gastrointestinal tract, nor have other similar attacks occurred since that time.

As previously mentioned, the patient was at home from the seventy-ninth to the two hundred and thirtieth postoperative day. For use during this interval, he was instructed in a qualitative diet containing approximately 408 Gm. of carbohydrate, 98 Gm. of protein and 102 Gm. of fat. He was asked to take 8 enteric-coated tablets of pancreatin with each meal. His weight remained at approximately 61 Kg.

The urine and feces were collected in six day samples. The dried weight of the stool and its content of nitrogen, fat, calcium and phosphorus were determined for periods I, II and III, and the average daily loss was computed. The urine was analyzed for nitrogen, sugar, calcium and phosphorus. The beginning and the end of the periods were marked by the use of carmine. The values for total and neutral fat were determined by the method of Saxon,[3] nitrogen by the method of Kjeldahl, carbohydrate by the method of Folin and Wu, calcium by the Clark-Collip modification of Kramer and Tisdall's method [4] and phosphorus by the method of Kuttner and Lichtenstein.[5]

Gross Character of Stools.—On each of the days of periods I and III (without pancreatin) one large, light-colored, fatty stool was passed. On each of the days on which pancreatin was administered, one stool was passed but the stool was smaller and darker than on other days. On the last of the six days during which pancreatin was taken, straining was required to pass the stool and bright red blood was noted. The darker color of the stool undoubtedly was partially due to the color of the enteric coating of the pancreatin tablets. It is of interest to note that the total lack of external pancreatic secretion did not produce frequent stools and that pancreatin changed the size and character of the stools. The patient later found that 8 tablets a day was sufficient to alter the gross character of the stools.

3. Hawk, P. B.; Bergeim, O.; Oser, B. L., and Cole, A. G.: Practical Physiological Chemistry, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 378.

4. Clark, E. P., and Collip, J. B.: The Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464 (March) 1925.

5. Kuttner, T., and Lichtenstein, L.: Micro Colorimetric Studies: II. Estimation of Phosphorus; Molybdic Acid-Stannous Chloride Reagent, J. Biol. Chem. **86**:671-676 (April) 1930.

Fecal Solids.—During periods I and III, the dry weight of the stool averaged respectively 90.73 and 91.97 Gm. a day (table 2). The dry weight of the feces was greater than that of normal subjects on the standard Schmidt test diet as reported by Pratt.[6] He found that the average daily weight of the dried feces of 6 normal persons over a period of three days was 54 Gm. and that the maximum was 62 Gm.

During periods I and III respectively fat composed 52.71 per cent and 49.99 per cent of the fecal solids, as is shown in table 2 (range

TABLE 2.—*Average Daily Values for Fecal Solids*

Period	Pancreatin Given	Total, Gm.	Fat, Gm.	Fat, per Cent of Total	Nitrogen as Protein, Gm.	Protein, per Cent of Total	Fat and Protein, per Cent of Total	Calcium, Gm.	Phosphorus, Gm.
I (12 days)	0	90.73	47.82	52.71	41.25	45.46	98.17	1.848	0.908
II (6 days)	+	58.33	24.73	42.40	21.88	37.51	79.91	2.550	1.500
III (6 days)	0	91.97	45.98	49.99	37.00	40.23	90.22	1.210	0.890

in normal persons on a general hospital diet, 8.5 to 28.5 per cent; average, 18.5 per cent).[7] During periods I and III respectively 30.93 and 37.52 per cent of the fecal fat was neutral fat (table 3).

In computation of the fecal nitrogen in terms of protein, the average daily protein (41.25 and 37 Gm.) accounted for 45.46 and 40.23 per cent of the fecal solids respectively in periods I and III; fat and protein accounted for 98.17 and 90.22 per cent of the fecal solids respec-

TABLE 3.—*Average Daily Value for Intake of Fat in Food and Loss in Feces*

Period	Pancreatin Given	Intake, Gm.	Loss in Feces, Gm.			Per Cent of Fecal Fat as		Per Cent of Intake Lost as		
			Neutral	Split	Total	Neutral	Fatty Acid	Neutral	Fatty Acid	Total
I (12 days)	0	100.5	14.79	33.03	47.82	30.93	69.07	14.72	32.86	47.58
II (6 days)	+	100.5	6.67	18.06	24.73	26.97	73.03	6.64	17.97	24.61
III (6 days)	0	100.5	17.25	28.73	45.98	37.52	62.48	17.16	28.59	45.75

tively in periods I and III. In spite of the interval of six months separating these two periods, the values are closely similar.

The average daily fecal solids during period II, while pancreatin was given, weighed 58.33 Gm. Fat composed 42.4 per cent of the fecal solids; of the total fat, 26.97 per cent was neutral fat. The average daily protein (21.88 Gm.) accounted for 37.51 per cent of the fecal solids; fat and protein accounted for 79.91 per cent. Thus, pancreatin

6. Pratt, J. H.: Pancreatic Disease: The Frank Billings Lecture, J. A. M. A. **120**:175-182 (Sept. 19) 1942.

7. Fowweather, F. S.: The Determination of the Amount and the Composition of the Fat of Faeces: I. Investigation of a "Wet" Method and Comparison with the "Dry" Method, Brit. J. Exper. Path. **7**:7-14 (Feb.) 1926.

reduced the average daily weight of the fecal solids approximately 35 per cent but did not change greatly the percentage of fat and nitrogen.

Reducing Substances in Feces and Urine.—Quantities of reducing substances in the feces were so small that they were not measured. The average daily values for reducing substances in the urine were 8.69 Gm. during period I, 14.4 Gm. during period II and 27.63 Gm. during period III.

Nitrogen in the Feces and Urine.—The intake and loss of nitrogen in the urine and feces are shown in table 4. Nitrogen loss in the

TABLE 4.—*Average Daily Values for Intake of Nitrogen in the Food and Loss in Urine and Feces*

Period	Intake, Gm.				Loss, Gm.			Balance, Gm.	Per Cent of Intake Lost in Urine	Per Cent of Intake Lost in Feces
	Pancreatin Given	Food	Pancreatin	Total	Urine	Feces	Total			
I (12 days)	0	19.3	....	19.30	12.09	6.60	18.69	+0.61	62.64	34.20
II (6 days)	+	19.3	1.68	20.98	13.96	3.50	17.46	+3.52	66.54	16.68
III (6 days)	0	19.3	....	19.30	12.82	5.92	18.74	+0.56	66.42	30.67

feces averaged 6.6 and 5.92 Gm. per day respectively in periods I and III (without pancreatin) and 3.5 Gm. per day during period II, when pancreatin was given. By the use of pancreatin, during period II, the average daily loss of nitrogen was reduced 3.1 Gm. from that of period I and 2.4 Gm. from that of period III. The daily loss of nitrogen in the urine was 12.09 and 12.82 Gm. respectively during periods I and III, without pancreatin, and 13.96 Gm. during period II, with pancreatin. The nitrogen balance was + 0.61 and + 0.56 Gm. a day respectively during periods I and III and +3.52 Gm. during period II. The loss of weight was 0.82 Kg. during period I and 0.87 Kg. during period III, but weight was gained (0.67 Kg.) during period II, while the patient was on the same diet with pancreatin. Total lack of external pancreatic secretion caused a large loss of nitrogen in the stools, but the nitrogen balance was slightly positive. The effect of the total lack of external pancreatic secretion observed in period III was remarkably similar to that observed six months earlier in the immediate postoperative period. Pancreatin given during period II reduced the loss of nitrogen in the feces by 47 per cent, as compared with that of period I, increased the nitrogen balance and converted a tendency toward loss of weight toward gain of weight.

Fat in the Feces.—The intake of fat averaged 100.5 Gm. a day in all three periods of observation (table 3). The average daily losses in the stools were 47.82 and 45.98 Gm. respectively in periods I and III (no pancreatin given) and 24.73 Gm. in period II (pancreatin given). The amount of fat that was lost in the stool was 47.58 and

45.75 per cent of the ingested fat during periods I and III and 24.61 per cent during period II. Part of the loss of fat may be attributed to the partial gastrectomy with end to side gastrojejunostomy. The fat lost in the stools as compared with the amount ingested after this surgical procedure averaged approximately 14 per cent in more than 10 cases, while the fat lost in the stools of normal persons on a high fat diet averaged about 4.5 per cent.[8] Most of the loss of fat in our case was due to lack of pancreatic secretion.

Neutral fat lost in the stools averaged 14.79 and 17.25 Gm. respectively in periods I and III (no pancreatin given) and 6.67 Gm. in period II (pancreatin given). Neutral fat composed 30.93 and 37.52 per cent of the total fat lost respectively in periods I and III and 26.97 per cent during period II.

The complete lack of external pancreatic secretion resulted in a large loss of fat, but splitting of fat was highly successful in spite of the absence of the pancreatic enzymes. This has been a matter of comment by Pratt[6] and others. The effect of the total lack of external pancreatic secretion observed in period III was remarkably similar to that observed six months earlier, during period I (immediate postoperative period). Pancreatin considerably reduced the loss of fat but did not produce much change of the percentage lost as neutral fat.

Effect of Loss of Food in Feces and Urine on Caloric Balance.—The caloric values of the ingested food and of the foods recovered in the urine and feces are shown in table 5. Metabolic fecal fat and nitrogen have been ignored in computation of the balance.

The average daily loss of calories was 590.88 in the feces and 34.76 in the urine in period I. This represented a loss of 23.9 per cent in the stools and 1.4 per cent in the urine, or 25.3 per cent in both feces and urine. There were 1,846.86 calories (only 166.86 calories more than the estimated basal needs) utilized, and a loss of weight of 0.82 Kg. occurred during this period. The data for period III are similar to those for period I. The loss of foodstuffs following total pancreatectomy was sufficiently great to affect nutrition and to increase the amount of food necessary for maintenance of weight.

Pancreatin reduced the caloric loss in the feces from 590.88 in period I to 310.1 in period II (the percentage of calories lost in the feces reduced from 23.9 in period I to 12.5 in period II), increased the calories utilized from 1,846.86 in period I to 2,104.8 in period II (257.94 calories) and reversed a slow loss of weight during period I, of 0.82 Kg. (averaging approximately 0.07 Kg. a day), to a gain of weight, of 0.67 Kg. during period II (approximately 0.11 Kg. a day).

8. Wollaegar, E. E.; Comfort, M. W.; Weir, J. F., and Osterberg, A. E.: The Total Solids, Fat and Nitrogen in the Feces: I and II, Gastroenterology **6**: 83-104 (Feb.) 1946.

TABLE 5.—*Average Daily Values for Calories Ingested and Lost in Urine and Feces*

Period	Pancreatin Given	Intake, Calories				Loss, Calories				Balance, Calories	Basal Requirement, Calories	Per Cent of Intake Lost in Feces and Urine
		Carbohydrate	Protein	Fat	Total	Fecal Fat	Fecal Protein	Urinary Sugar	Total			
I (12 days)	0	1,085.6	482.4	904.5	2,472.5	425.88	165.0	34.76	625.64	1,846.86	1,680.0	25.3
II (6 days)	+	1,085.6	482.4	904.5	2,472.5	222.60	87.5	57.60	367.70	2,104.80	1,680.0	14.9
III (6 days)	0	1,085.6	482.4	904.5	2,472.5	413.82	148.0	110.52	672.34	1,800.16	1,680.0	27.2

TABLE 6.—*Values for Plasma Lipids (Cholesterol, Cholesterol Esters, Lecithin, Fatty Acids, Total Lipids), Serum Calcium, Phosphorus, Protein and Bilirubin, Albumin-Globulin Ratios, Sulfobromophthalein Tests of Hepatic Function, Hemoglobin Levels and Erythrocyte and Leukocyte Counts*

Determination	Normal Values			Postoperative Day												
	Low	High	Average	4th	15th	25th	30th	36th	42d	50th	60th	69th	75th	231st	242d	250th
Plasma lipids, mg. per 100 cc. plasma																
Cholesterol	175	354	244	...	200	300	267	210	234	203	234	247	267	237	320	237
Cholesterol esters	120	268	174	...	120	153	159	147	172	142	90	164	124	151	181	156
Lecithin	185	309	235	...	277	369	357	332	380	309	318	269	380	347	277	238
Fatty acids	253	579	384	...	415	814	802	712	583	581	592	532	783	459	478	471
Total lipids	461	827	628	...	615	1,114	1,060	922	817	784	826	779	1,050	696	708	708
Calcium, mg. per 100 cc. serum	9.0	11.0	...	...	8.4	10.0	9.9	...	10.4	10.3	10.6	...	10.7	10.1	10.7	...
Phosphorus, mg. per 100 cc. serum	3.0	4.0	...	...	...	5.7	4.6	...	3.8	4.0	4.0	...	4.8	3.5	3.7	...
Bilirubin, mg. per 100 cc. serum																
Direct	...	...	...	0	...	...	...	...	...	0	0	...	0	0	...	...
Indirect	...	0.6	...	0.9	...	...	...	...	...	0.3	0.2	...	0.4	1.3	...	...
Protein, Gm. per 100 cc. serum	6.0	8.0	...	6.1	5.9	6.8	7.0	7.0	7.9	7.3	7.1	...	8.1	7.6	7.6	...
Albumin-globulin ratio	1.5:1	3:1	...	...	1.3:1	1.19:1	1.28:1	1.24:1	1.10:1	1.19:1	...	...	1.26:1	1.5:1	1.44:1	...
Sulfobromophthalein test of hepatic function	...	...	...	0	...	0	0	0	0	0	1	...	0	0	...	...
Hemoglobin, Gm. per 100 cc. blood	14.0	17.0	...	9.0	10.45	10.45	10.45	11.5	11.8	11.05	10.9	12.4	12.0	11.9	13.8	...
Erythrocytes * per cu. mm	4.25	5.25	...	...	3.59	3.00	3.64	4.10	4.33	4.12	3.8	3.9	4.6	4.67	4.85	...
Leukocytes per cu. mm	5,000	9,000	...	23,400	12,100	8,400	6,700	12,200	10,800	9,000	6,400	8,600	7,000	14,200	11,200	...

* Million.

Effect of Total Lack of External Pancreatic Secretion on Loss of Calcium and Phosphorus in Feces and Urine.—The average daily content of calcium and phosphorus in the diet was respectively 2.5 and 2.3 Gm. during periods I and III. The daily loss in the urine averaged 0.216 and 0.38 Gm. of calcium and 1.086 and 1.43 Gm. of phosphorus respectively in periods I and III and the daily loss in the feces averaged 1.85 and 1.21 Gm. of calcium and 0.908 and 0.89 Gm. of phosphorus respectively during periods I and III. Although the data are not reliable for calcium and phosphorus balances, it appears that the loss of calcium in the feces while the patient was receiving 2.5 Gm. a day was not excessive, in spite of the large loss of fat in the feces. It is generally accepted, on the contrary, that poor utilization of fatty acids and fats interferes with absorption of calcium because it leaves fatty acids in the intestine to form insoluble calcium soaps.[9] The daily excretion of calcium in the urine was of sufficient magnitude to suggest a reasonably normal absorption of calcium from the gastrointestinal tract.

EFFECT OF TOTAL PANCREATECTOMY ON BLOOD LIPIDS AND HEPATIC FUNCTION

The values for plasma lipids, serum calcium, phosphorus, bilirubin and proteins, the albumin-globulin ratios, the degree of dye retention on sulfobromophthalein tests for hepatic function, the hemoglobin levels and the erythrocyte and leukocyte counts secured during the postoperative periods of observation are given in table 6. The values for plasma lipids in persons of the same age group[10] as our patient, the normal values for serum calcium, phosphorus and protein and the normal albumin-globulin ratios also are shown in table 6.

The total fat and cholesterol were determined by the method of Bloor,[11] lecithin by the method of Youngburg and Youngburg,[12] cholesterol esters by the method of Bloor and Knudson,[13] calcium by the Clark-Collip[4] modification of the Kramer and Tisdall method, phosphorus by the method of Kuttner and Lichtenstein,[5] bilirubin by

9. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, chap. 16, pp. 805-861.

10. Barker, N. W.: The Plasma Lipoids in Arteriosclerosis Obliterans, Ann. Int. Med. **13**:685-692 (Oct.) 1939.

11. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227-231, 1916; The Determination of Small Amounts of Lipid in Blood Plasma, ibid. **77**:53-73 (April) 1928.

12. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: I. A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. **16**:158-166 (Nov.) 1930.

13. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107-112, 1916.

the method of Sepulveda and Osterberg,[14] protein by the mass Kjeldahl method and the albumin-globulin ratio by the Kingsley method.[15]

It is interesting to note that definite hyperlipemia developed by the twenty-fifth postoperative day. The rise of values for cholesterol and cholesterol esters was of short duration and was not great enough to pass the upper limits of the so-called normal range of values. The rise of values for lecithin, fatty acids and total lipids was persistent and of sufficient magnitude to exceed the upper limits of normal range of values. These concentrations remained near or above the upper limits through the seventy-fifth postoperative day. Insulin was withheld on the sixty-seventh, sixty-eighth and sixty-ninth postoperative days, without definite effect on the concentration of plasma lipids on the sixty-ninth day. The values for plasma lipids declined in the interval between the seventy-fifth and the two hundred and thirty-first postoperative day. On the two hundred and thirty-first, two hundred and forty-second and two hundred and fiftieth postoperative days the values were within the range found in normal persons of the same age group. Withholding of insulin on the two hundred and forty-fifth, two hundred and forty-sixth and two hundred and forty-seventh postoperative days did not noticeably affect the level of concentration of plasma lipids as obtained on the two hundred and fiftieth day.

Hepatic function was satisfactory throughout the period of study. The serum bilirubin remained normal, and the van den Bergh reaction was indirect. The serum proteins increased, reaching high normal values toward the end of the period of observation. The albumin-globulin ratio also became normal. A sulfobromophthalein test of hepatic function did not disclose dysfunction except in one test, on the sixtieth postoperative day, when retention of dye occurred. The retention was only 6 per cent (upper limit of normal 5 per cent) and was transitory. It is doubtful whether this retention of dye was significant.

Total pancreatectomy produced dissimilar results in our patient from those following total pancreatectomy in dogs. When a depancreatized dog is maintained with insulin and a diet adequate to maintain a normal dog, infiltration of the liver with fat, decreased requirement for insulin, decreased output of sugar in the urine and about a 50 per cent reduction in blood fats develop.[16] These changes may take place

14. Sepulveda, B., and Osterberg, A. E.: Serum Bilirubin: Procedure for Determination of Indirect and Direct Values, J. Lab. & Clin. Med. **28**:1359-1368 (Aug.) 1943; correction, ibid. **28**:1654 (Oct.) 1943.

15. Kingsley, G. R.: A Rapid Method for the Separation of Serum Albumin and Globulin, J. Biol. Chem. **133**:731-735 (May) 1940.

16. Dragstedt, L. R.: Some Physiologic Problems in Surgery of the Pancreas, Ann. Surg. **118**:576-589 (Oct.) 1943. Dragstedt, L. R.; Clark, D. E., and Ver-

(Footnote continued on next page)

within four to five weeks or earlier and are well developed by the twentieth week. The reduced function of the liver is measurable with the sulfobromophthalein test.[17] These findings have appeared when the depancreatized dog has been fed a high protein, low carbohydrate, low fat diet,[18] a high protein, high carbohydrate, low fat diet [19] or a high protein, high fat (40 per cent) diet,[20] with or without vitamin supplements. A lipotropic substance, either raw pancreas, lipocaic, lecithin or choline, must be added to prevent these changes. Dragstedt has found that the minimal effective daily dose of choline for a dog weighing 9 to 14 Kg. is about 1 Gm.[21]

In the case reported in this paper, the patient received first a mixed diet containing about 270 Gm. of carbohydrate, 108 Gm. of protein and 100 Gm. of fat and later a mixed diet containing about 400 Gm. of carbohydrate, 100 Gm. of protein and 100 Gm. of fat with insulin and was not given raw pancreas, lipocaic, choline or pancreatin during the first five weeks. Hyperlipemia instead of hypolipemia developed and hepatic dysfunction, indicating infiltration of the liver with fat, did not appear. After the thirty-sixth postoperative day, the patient received 15 Gm. and later 10 Gm. of enteric-coated pancreatin, and by the two hundred and fiftieth postoperative day he still did not show hypolipemia or disturbed hepatic function.

On the basis of comparative weights (130 pounds [59.0 Kg.] for our patient and 26½ pounds [12 Kg.] for the dog) and calculating roughly from the amount of choline necessary to prevent the typical

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meulen, C.: The Significance of Lipocaic in Surgery, ibid. **110**:907-914 (Nov.) 1939. Dragstedt, L. R.: The Present Status of Lipocaic, J. A. M. A. **114**:29-32 (Jan. 6) 1940. Rubin, S. H., and Ralli, E. P.: The Effect of Depancreatization and Ligation of the Pancreatic Ducts on the Blood and Liver Lipids of Dogs, Am. J. Physiol. **129**:578-584 (June) 1940.

17. Goodpasture, W. C.; Vermeulen, C.; Donovan, P. B., and Dragstedt, L. R.: The Bromsulphalein Liver Function Test as a Method of Assay of Lipocaic, Am. J. Physiol. **124**:642-646 (Dec.) 1938.

18. Montgomery, M. L.; Entenman, C., and Chaikoff, I. L.: The Liver Lipids of Dogs Subjected to Ligation of the External Pancreatic Ducts, J. Biol. Chem. **128**:387-398 (May) 1939.

19. Best, C. H.; Hershey, J. M., and Huntsman, M. E.: The Control of the Deposition of Liver Fat, Am. J. Physiol. **101**:7 (June) 1932. Ralli, E. P.; Flaum, G., and Banta, R.: The Results of Feeding Lecithin and Pancreas in Depancreatized Dogs on the Liver Fat and Its Saponifiable and Unsaponifiable Fractions, ibid. **110**:545-551 (Jan.) 1935. Montgomery and others.[18]

20. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**:175-181 (Sept.) 1936.

21. Van Prohaska, J.; Dragstedt, L. R., and Harms, H. P.: The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatized Dog, Am. J. Physiol. **117**:166-174 (Sept.) 1936.

changes in the depancreatized dog, our patient needed about 5 Gm. of choline a day to protect him against the development of a fatty liver and hypolipemia. Apparently he received much less than this. On the basis of a diet containing 100 Gm. each of green beans, carrots, asparagus and rice, 200 Gm. of Irish potatoes, 120 Gm. of bread, 700 Gm. of whole milk, 2 egg yolks and 150 Gm. of meat, the patient received each day approximately 1.8 Gm. of choline, according to the values for choline in various foodstuffs supplied by Engel [22] and by McIntire, Schweigert and Elvehjem.[23] To this was added, after the thirty-sixth postoperative day, the amount of choline and lipocaic present in the pancreatin. Each tablet of concentrated pancreatin of the manufacture used (Wilson Laboratories) contains 1.8 mg. of choline.[24] On the basis of 30 tablets a day (the approximate dose used during most of the period of observation), the pancreatin added only 54 mg. of choline a day to that obtained in the diet. It is of interest to note in passing that pancreatin is a poor source for choline, since approximately 140 tablets of pancreatin are needed to supply the choline in 1 egg yolk. The pancreatin given to this patient contained an amount of choline too small to influence significantly the development of infiltration of the liver with fat.

Dragstedt [25] has found that 10 Gm. of pancreatin supplies an effective daily dose of lipocaic to the average-sized depancreatized dog. Again, on a comparative basis of weights, the amount of lipocaic given to the patient appears inadequate.

The possibility that in the case reported in this paper the changes appearing in the depancreatized dog may ultimately develop has not been forgotten. A satisfactory explanation, in the light of experience with the depancreatized dog, of the failure of hypolipemia and infiltration of the liver with fat to develop in the case of this depancreatized human being, as well as 10 per cent of depancreatized dogs, is not readily found. It would be interesting to know whether hyperlipemia existed before the development of carcinoma of the pancreas and before pancreatectomy. Attention may be called to the fact that the spleen, the duodenum and part of the stomach in addition to the pancreas were removed from our patient whereas only the pancreas was removed from the depancreatized dog, but this difference does not appear at this time to explain the difference in results so far obtained. It seems

22. Engel, R. W.: Modified Methods for the Chemical and Biological Determination of Choline, J. Biol. Chem. **144**:701-710 (Aug.) 1942; The Choline Content of Animal and Plant Products, J. Nutrition **25**:441-446 (May) 1943.

23. McIntire, J. M.; Schweigert, B. S., and Elvehjem, C. A.: The Choline and Pyridoxine Content of Meats, J. Nutrition **28**:219-223 (Oct.) 1944.

24. Klein, D.: Personal communication to the authors.

25. Dragstedt, L. R.: Personal communication to the authors.

more likely that the differences between the diets given to our patient and those given to the depancreatized dog may be important. The comment of McHenry and Patterson,[26] in their recent review of lipotropic factors, that "The present situation with regard to the cause and prevention of fatty livers in depancreatized dogs is that there are a number of unanswered questions" seems to apply equally to the depancreatized human being.

Certain abnormal morphologic characteristics of the cellular elements of the blood were noted. Macrocytosis due to increased regeneration and Howell's bodies (presumably due to splenectomy) were observed. The myeloid immaturity, which extended to the premyelocytes, was difficult to explain, since there was no evidence of metastasis. This blood picture was essentially the same in the late period of observation, except for fewer macrocytes. The number of erythrocytes and the amount of hemoglobin returned gradually to a normal level.

SUMMARY AND CONCLUSIONS

The studies reported in this paper on the effect of the lack of internal and external secretions of the pancreas in a totally depancreatized human being were performed as a pilot study for future work on the problem. From the cases of pancreatectomy presented in the literature[27] and from those in which it was performed at the Mayo Clinic, it would seem that a depancreatized adult requires about 20 to 70 units of insulin daily during the first week or so after operation and about 25 to 40 units daily for maintenance thereafter. Whereas the severity of diabetes may be determined superficially by the amount of insulin needed for a given degree of control, the tendency of persons who have diabetes mellitus toward the development of ketosis varies tremendously.

The changes in the blood and urine during two periods of insulin privation of eighty-nine hours each in the case of a diabetic man who underwent total pancreatectomy because of an adenocarcinoma, grade 2 (Broders' method), were as follows: When 440 Gm. of carbohydrate were given the ketonemia was slight, and when 125 Gm. were given the ketonemia was pronounced. These data, with respect to the diabetic status before and after pancreatectomy, are presented as a contribution to our knowledge of diabetes in depancreatized man.

Total pancreatectomy did not produce diarrhea in spite of the large amount of fat in the stools. The bulkiness of the stools was reflected

26. McHenry, E. W., and Patterson, J. M.: Lipotropic Factors, Physiol. Rev. **24**:128-167 (Jan.) 1944.

27. Fallis, L., cited by McClure, R. D., in discussion on Brunschwig, A.: The Surgical Treatment of Carcinoma of the Body of the Pancreas, Ann. Surg. **120**: 406 (Sept.) 1944.

in abnormally high values for their dry weight. Fat and protein in the feces accounted for most of their dry weight.

Total pancreatectomy was followed by considerable reduction in digestion and absorption of protein and fat. About a half of the ingested fat and about a third of the ingested protein were lost in the feces. Digestion of fat was surprisingly good, as only about a third of the fat in the feces was neutral fat. The absorption of calcium and phosphorus was apparently adequate in spite of the high loss of foodstuffs in the stools.

Concentrated pancreatin in enteric-coated tablets (15 with each meal, or 15 Gm. daily) was found to reduce the loss of fat and protein by approximately 50 per cent. It also reduced the dry weight of the feces and altered the gross appearance of the stool. Concentrated pancreatin reduced the loss of calories sufficiently to cause the patient to gain weight slightly over the short period of study rather than lose weight. The amounts of fat and nitrogen lost in the feces even when pancreatin was given were in excess of normal values. Although concentrated pancreatin in the doses given was not a complete substitute for external pancreatic secretion, it was definitely valuable in maintaining the nutrition of the patient.

In our case, total pancreatectomy was not followed during the eight months of observation by a decrease in the amount of glucose lost in the urine or of the insulin requirements or by hypolipemia and hepatic dysfunction indicative of a fatty liver, as is often the case in pancreatectomized dogs. On the contrary, the patient's diabetes remained of about the same severity, the protamine zinc insulin requirement being approximately 40 units a day. Hepatic function as measured by the sulfobromophthalein test remained unimpaired throughout the eight months of observation, and hyperlipemia rather than hypolipemia appeared. The patient remained in good health and maintained his weight while taking a mixed diet plus insulin and 10 Gm. of concentrated pancreatin. His condition was reported as good twelve months after operation.

PARENTERAL ADMINISTRATION OF FLUIDS DURING THE EARLY CARE OF BATTLE CASUALTIES

LIEUTENANT E. E. MUIRHEAD (MC), U.S.N.R.

LIEUTENANT M. H. GROW (MC), U.S.N.R.
AND
CAPTAIN A. T. WALKER (MC), U.S.N.

THE manner of handling the administration of parenteral fluid needed during the early care of a series of closely observed battle casualties constitutes the basis for this report.

The casualties occurred in the New Guinea, Bismarck Archipelago and Philippine areas. Observations were conducted mainly aboard an LST acting as a casualty ship during the early phases of amphibious operations. Casualties were received from ships damaged during the landing phases and from troops landed on the invasion beaches.

TYPES OF CASES

An analysis of cases of 345 patients will be made (6.8 per cent of the total patients treated). Tables 1, 2 and 3 contain information concerning the types of injuries encountered.

TABLE 1.—*Frequency of Types of Injuries*

Types of Injuries	Cases	
	Number	Percentage
Fractures and lacerations	108	31.3
Lacerations; no fracture	100	28.98
Abdominal injuries	25	7.24
Thoracic injuries	11	3.18
Head injuries	7	2.02
Burns	94	27.24
Total	345	99.96

In table 1 the frequency of the types of injuries is given. Outside the group with burns 51.2 per cent of the patients sustained multiple injuries, that is, multiple lacerations of skin, muscles or other parts, with or without fractures. The group with abdominal injuries included patients with perforation of the abdominal wall and injury

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to one of the viscera; the group with thoracic injuries sustained perforation of the thoracic cage; the group with head injuries presented injury about the head and mental and/or neurologic signs. The group with fractures can be further subdivided into patients with fractures of extremities (92.5 per cent [femur 27 per cent, tibia 40 per cent and upper extremities 33 per cent]) and patients with compound fractures (78 per cent).

There are two types of information in table 2, expressed on the basis of frequency distribution: (1) the time interval between the occurrence of the injury and the first observation by us and (2) the specific gravity values of whole blood and serum prior to therapy, distributed as to level and in relation to the time since injury.

The patients are divided into two groups: group I, with lacerations, with or without fractures, and group II, with burns, with or without involvement of subcutaneous tissues.

The percentages of patients seen within forty-eight hours or less following the injury were 62.2 per cent for group I and 88.4 per cent for group II. In accordance with previously established normal ranges,[1] certain observations can be additionally made. In group I, 88.85 per cent of the patients displayed a specific gravity of the blood in the lower limits of normal or below, and 66.5 per cent had values definitely below normal; 98.6 per cent displayed a specific gravity of the serum at the lower limits of normal or below, and 60.5 per cent had values definitely below normal. Of the patients definitely below normal for specific gravity of the blood, 16.1 per cent were seen between one-half hour and eight hours, 40.6 per cent between nine and forty-eight hours and 43.2 per cent after forty-eight hours; for specific gravity of the serum the corresponding figures are 16.6 per cent, 42 per cent and 41.3 per cent.

In group II, 71.2 per cent of the patients had specific gravities of the blood in the upper limits of normal or beyond and 25.5 per cent had values definitely above normal but only 4.2 per cent had specific gravities of the serum in the upper limits of normal or beyond; 28.7 per cent demonstrated blood values at lower limits of normal or below, the corresponding figure for specific gravity of the serum being 41.4 per cent.

In table 3 an indication of the volume of various fluids given to patients with the different types of injuries is given. The greatest volumes of blood were given to the group with "lacerations-fractures," whose specific gravity values were lowered, and the greatest volumes

1. Muirhead, E. E.; Grow, M. H., and Walker, A. T.: Practical Observations on the Copper Sulphate Method for Determining the Specific Gravities of Blood and Serum, Surg., Gynec. & Obst. **82**:405-413 (April) 1946.

TABLE 2.—*Time Interval Between Injury and Treatment and Specific Gravity Values*

Time from Injury to Observation	Specific Gravity, Blood	Specific Gravity, Serum	Number of Patients with Lacerations—Fractures: 1.030 to 1.040+ / 1.020 to 1.022+	1.041 to 1.050+ / 1.023 to 1.024+	1.051 to 1.055+ / 1.025 to 1.027+	1.056 to 1.060+ / 1.028 to 1.030	1.061+ / 1.030+	Total	Number of Patients with Burns: 1.030 to 1.040+ / 1.020 to 1.022+	1.041 to 1.050+ / 1.023 to 1.024+	1.051 to 1.055+ / 1.025 to 1.027+	1.056 to 1.060+ / 1.028 to 1.030	1.061+ / 1.030+	Total
0.5 to 8+ hrs.	B		2	23	15	7	..	47	..	..	..	6	8	14
	S		4	18	22	..	..	44	..	..	7	4	..	11
9 to 24+ hr.	B		7	26	19	4	..	56	..	..	5	10	8	23
	S		7	21	24	1	..	53	3	9	16	..	..	28
25 to 48+ hr.	B		10	20	5	6	1	42	..	1	11	27	7	46
	S		10	18	13	1	..	42	5	15	24	..	..	44
49 to 72 hr.	B		6	11	2	3	..	22	..	3	1	..	1	5
	S		4	10	6	..	..	20	2	1	..	..	..	3
3 to 5+ days	B		8	12	3	1	..	24	..	2	1	..	..	3
	S		12	8	4	..	..	24	2	..	1	..	..	3
6 to 10+ days	B		7	16	6	4	..	33	..	..	1	..	..	1
	S		7	14	8	1	..	30	..	1	..	..	..	1
11 to 20 days	B		..	7	2	..	..	9	..	1	1	..	..	2
	S		..	..	6	..	..	6	..	1	1	..	..	2
Total	B		40	115	52	25	1	233	..	7	20	43	24	94
	S		44	89	83	3	..	219	12	27	49	4	..	92

of normal plasma and concentrated albumin were given to the patients in the group with "burns." Notice that larger volumes were frequently considered necessary to cope with the deviations of the criteria used for the appraisal of fluid needs.

TABLE 3.—*Volume of Fluids Given Patients in Different Types of Cases*

Types of Cases	Blood (Citrated), Cc.					
	500 to 900+	1,000 to 1,900+	2,000 to 3,000+	3,100 to 4,000+	Total Cases	Total Volume, Cc.
Laceration and fractures						
Specific gravity near normal	6	15	1	1	23	29,650
Shock, specific gravity low	1	14	14	8	37	93,275
Anemia, etc., specific gravity low	7	18	27	6	58	112,200
Burns						
Specific gravity near normal	..	2	1	..	3	4,300
Shock, etc., specific gravity high	1	1	2	..	4	6,355
Total	15	50	45	15	125	245,780

Types of Cases	Plasma (Normal), Cc.					
	250 to 500+	600 to 900+	1,000 to 2,000+	2,100 to 3,000+	Total Cases	Total Volume, Cc.
Laceration and fractures						
Specific gravity near normal	28	8	14	2	52	39,000
Shock, specific gravity low	8	4	13	3	28	38,825
Anemia, etc., specific gravity low	9	5	18	2	34	30,450
Burns						
Specific gravity near normal	26	8	7	1	42	27,150
Shock, etc., specific gravity high	2	1	17	7	27	64,200
Total	73	26	69	15	183	199,625

Types of Cases	Dextrose in Isotonic Solution of Sodium Chloride (5 per Cent), Cc.					
	1,000 to 1,900+	2,000 to 2,900+	3,000 to 4,000+	4,100 to 5,000+	Total Cases	Total Volume, Cc.
Laceration and fractures						
Specific gravity near normal	15	1	2	1	19	27,000
Shock, specific gravity low	3	2	..	1	6	13,900
Anemia, etc., specific gravity low	3	3	1	1	8	16,600
Burns						
Specific gravity near normal	6	..	1	..	7	9,000
Shock, etc., specific gravity high	5	3	2	..	10	17,500
Total	32	9	6	3	50	84,000

Types of Cases	Albumin * (Concentrated Solution), Cc.					
	100	200	300 to 400+	500+	Total Cases	Total Volume, Cc.
Laceration and fractures						
Specific gravity near normal	2	3	2	1	8	2,100
Shock, specific gravity low	2	2	5	2	11	3,100
Anemia, etc., specific gravity low	1	4	..	..	5	900
Burns						
Specific gravity near normal	1	5	2	..	8	1,800
Shock, etc., specific gravity high	2	4	7	5	18	9,885
Total	8	18	16	8	50	17,785

* In addition 3,550 cc. of concentrated plasma (threefold or fourfold) were administered to 8 patients.

For the purpose of this paper, the patients are divided into two main categories: (1) those with loss of blood following the trauma (hemorrhagic type) and (2) those with loss of plasma (plasmorrhagic type). Casualties in group 1 had various degrees of lacerations, with or without fractures, or crushing injuries, with torn-open blood vessels. Group 2 was composed primarily of patients with burns, resulting in increased capillary permeability.

The time interval between injury and arrival aboard the casualty ship was used to subdivide each group additionally: (*a*) patients observed during the first twenty-four or thirty-six hours, when "shock" was more apt to occur (except in cases in which major operations were performed later and a new such "shock period" was considered), and (*b*) patients first observed after thirty-six to forty-six hours, when more stabilized grades of circulatory compensation had occurred. For the latter patients the emphasis was shifted toward the replenishment of specific elements which had been lost (red cells, proteins, salts and vitamins) and toward the supply of metabolic needs. These replacements were needed to encourage healing of wounds, to combat infection and to prevent the wastage of body tissues. Although no sharp line of demarcation can be drawn, this categoric separation into clinical types seemed worth while despite variable degrees of overlapping.

CRITERIA FOR APPRAISAL OF CASES

The appraisal of needs for parenteral administration of fluid was based on four major criteria. Emphasis was placed on the repeated comparisons of the more relevant features of these criteria.

I. *Clinical Picture.*—A grouping of strictly clinical features is discussed in five phases:

A. History: In taking the history, emphasis was placed on circumstances surrounding the injury, traumatizing agent, time of injury, blood loss, previous therapy (blood, plasma, morphine and operations), unconsciousness and special or localizing complaints, such as loss of sensation in a foot.

B. Physical Findings: Besides the usual physical examination, main interest was centered in:

1. Site of injury. This included location, type and condition of wounded parts.

2. Volume of pulse. This was considered much more important than the pulse rate.

3. State of veins. The degree of conspicuousness of superficial veins below the heart was related to the loss of blood volume in "shock." This was compared with the volume of blood or blood substitute necessary to effect recovery. The usual concept of the compensatory mechanism in severe loss of blood embraces a general vasoconstriction during oligemia which is greater in the somatic zones (skin, subcutaneous tissue and muscle) than in the vital organs, thus protecting visceral areas (brain, heart, lungs, liver, kidneys and other organs).

While plasma, albumin solution or citrated blood was administered, it was not considered necessary to become concerned over the volume given, so long as the veins were closely observed. Blood and blood derivatives were given until the peripheral veins showed normal filling. The opposite extreme to shock (volume overload) is difficult to attain in casualties who have lost large amounts of circulating volume. The latter condition is characterized by obvious venous engorgement and pulmonary rales in dependent areas.

4. State of skin. A change from the characteristic fulness and spongy recoil of normally hydrated skin (persons of military age) to dryness, stickiness and ridging when pinched were taken as the obvious signs of loss of tissue turgor.

Experimental dehydration has demonstrated the loss of water from large stores in the skin, subcutaneous tissues and muscles first, vital organs being protected until late.[2] Dogs acutely dehydrated with 50 per cent dextrose lose cutaneous turgor rather late.[3]

Casualties observed during early hours and those able to take water orally seldom exhibited loss of cutaneous turgor. This state of adequate hydration was considered the explanation for the prompt effectiveness of concentrated protein solutions (albumin and plasma) in coping with oligemia in freshly wounded casualties or those able to ingest adequate amounts of fluid.

Other cutaneous signs used in detection of shock were pallor, sweating and cyanosis.

5. Other observations included the state of the respiratory system, the condition of the pupils (morphine), the presence or absence of fever, the presence of devitalized limbs and roentgenologic examinations when possible.

C. Mental State: The main cerebral signs in shock were disorientation, restlessness, dulness and coma. In the absence of injury to the head, these signs were considered extremely important. These signs diminished only after the circulating volume had been reestablished.

D. Renal State: Return to normal urinary output and specific gravity were taken as the main indications of an adequate water intake and rehydration. This return to normal was observed in most cases after the correction of the oligemia.

The presence of albumin, red cells and casts in the urine indicated a poor prognosis; the gravity of the prognosis increased with persistence of these urinary findings.

E. Dietary Needs: Persons unable or unwilling to ingest enough food by mouth required supplements given parenterally. Protein as plasma protein, dextrose, salts and vitamins were administered in varying quantities. Two factors were constantly considered: 1. Severely burned and severely injured patients frequently require two to three times the normal daily protein intake. 2. Infused red cells not only serve their specific functions but in cases of depletion spare proteins for other purposes (replenishment of protein stores, increase in circulating plasma proteins, repair of wounds and combat of infections). This is in accordance with the concept of Whipple and Madden.[4]

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2. Flemister, L. J.: Distribution of Available Water in Animal Body, Am. J. Physiol. **135**:430-438 (Jan.) 1942.

3. Muirhead, E. E., and Hill, J. M.: Unpublished data.

4. Whipple, G. H., and Madden, S. C.: Hemoglobin Plasma Protein and Cell Protein—Their Interchange and Construction in Emergencies, Medicine **23**: 215-224 (Sept.) 1944.

II. *Blood Pressure.*—Naturally blood pressure, a variable finding, was of greatest value when lowered in a shock suspect. A pressure that was depressed for thirty minutes in a wounded man was considered to have been effected by more than neurogenic influences. Oligemia was found to be the main reason for a significant drop in blood pressure. Hypertensive intervals in hemorrhagic patients were observed to be transient in a low percentage of cases and were usually followed by sudden drops to critically hypotensive levels. With the blood pressure at normal levels, appraisal of the severity of the shock rested on other criteria.

III. *Concentration Studies.*—A preliminary consideration of the measurements of specific gravity by the copper sulfate method conducted in these cases has been made.[1] These studies reflect the concentration of red cells and proteins in unit volumes of blood and serum respectively. In wounded men with normal or near normal hydration, the persistent dilution of these elements was taken as indicative of a lowering in the total bulk of these elements. The concentration of red cells in the cases of burns was indicative of a lowered plasma volume and a decrease in the bulk of circulating proteins.

In the absence of rapid means of determining the total bulk of red cells and proteins, this method became extremely important. Attempts were made to administer the appropriate fluid and to regulate its quantity to rectify the persisting abnormalities in the specific gravity values.

IV. *Response to Therapy.*—This criterion was utilized during the administration of various fluids by the periodic reapplication of the first three criteria.

RATIONALE FOR FLUIDS USED

The main indications for the use of the five separate fluids are outlined:

1. Citrated blood (1:5 dilution, with citrate-dextrose preservative):

(*a*) To increase the oxygen-carrying capacity of the circulating blood in hemorrhagic "shock," posthemorrhagic anemia and postburn anemia.

(*b*) To spare proteins, which otherwise would be used to manufacture red cells, for other purposes.

(*c*) To provide essential red cell–building material for patients unable to ingest these materials (patients with abdominal injuries, facial-neck injuries and similar injuries).

(*d*) To combat other types of anemias.

2. Concentrated albumin (25 Gm. per hundred cubic centimeters) and concentrated plasma (threefold or fourfold):

(*a*) To rectify oligemia rapidly, especially in the severer grades of shock, hemorrhagic or plasmorrhagic, as previously discussed.[5]

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5. Hill, J. M.; Muirhead, E. E.; Ashworth, C. T., and Tigertt, W. D.: The Use of Desiccated Plasma, with Particular Reference to Shock, J. A. M. A. **116:** 395-402 (Feb. 1) 1941. Muirhead, E. E., and Hill, J. M.: The Advantages and Clinical Uses of Desiccated Plasma, Ann. Int. Med. **16:**286-302 (Feb.) 1942. Erf, L. A., and Jones, H. W.: Experiences Associated with Transfusion Unit in Seven Hundred Bed Hospital: Annual Survey of Over 3,500 Administrations of Blood and Plasma (Dried), ibid. **19:**1-27 (July) 1943. Ashworth, C. T.; Muirhead, E. E., and Hill, J. M.: The Effect of Hypertonic Plasma on Body Fluids in Normal Experimental Animals, Am. J. Physiol. **136:**194-199 (March) 1942.

(*b*) To replenish proteins in hypoproteinemia.

3. Normal plasma (5 to 6 Gm. per hundred cubic centimeters):

(*a*) To treat shock, but slower than the concentrated solutions in action and the administration of comparable amounts of protein.

(*b*) To supplement dietary protein and salts.

(*c*) To supplement salt and dextrose solutions in dehydrated and suspected dehydrated patients as per previous discussions.[6]

4. Five per cent dextrose in isotonic solution of sodium chloride:

(*a*) To supplement sugar and salt intake; usually given with thiamine hydrochloride.

(*b*) To replace fluid in cases in which excessive fluid loss had occurred (Wangensteen suction, restricted oral intake and other causes).

(*c*) In the presence of oliguria in which oligemia and major nephropathy were not directly suspected.

5. Five per cent dextrose in distilled water:

(*a*) To encourage urinary output; often alternated with isotonic solution of sodium chloride.

(*b*) As a means of administering carbohydrate; usually given with thiamine hydrochloride.

ILLUSTRATIVE CASES

The salient features of several cases are given to illustrate the foregoing discussion.

The term "shock" is used to cover mainly the hemodynamic abnormalities due to oligemia and reflected by such well known signs as weak pulse, lowered blood pressure, poor filling of veins, pallor, sweating, coldness of the skin, mental confusion and dulness and oliguria.

The specific gravity values were considered definitely abnormal when found to be outside previously established ranges.[1] These ranges for blood were 1.0543 to 1.0619 and for serum 1.0247 to 1.0299. The blood pressure as given signified millimeters of mercury, and the pulse rate signified beats per minute.

I. *Hemorrhagic Group.*—A. Patients Seen Within Twenty-Four to Thirty-Six Hours after Injury (Shock Period): 1. With normal or near normal criteria. The subsequent uneventful course in cases of this type provided justification for the discussed criteria.

CASE 1.—A man was seen two to three hours after injury, with a shrapnel perforation of the abdominal wall and signs of peritoneal irritation. No signs of shock were apparent; the blood pressure was 120 systolic and 70 diastolic, and the specific gravities were 1.053 (whole blood) and 1.027 (serum). At operation no

6. Hill, J. M., and Muirhead, E. E.: The Use of Desiccated Plasma in Urology, J. Urol. **47**:387-394 (March) 1942. Muirhead, E. E.; Hill, J. M., and Ashworth, C. T.: The Use of Human Plasma Protein Solutions in Surgery, South. Surgeon **11**:414-431 (June) 1942.

excessive peritoneal hemorrhage was found, but a perforation of the small bowel was discovered and repaired. The patient progressed nicely and was transferred from the casualty ship in good condition. No special fluid was given.

Case 2.—A man was seen thirty minutes after injury, with a shrapnel wound of the abdomen. There were no signs of shock; the specific gravities were 1.057 (whole blood) and 1.025 (serum). At laparotomy no peritoneal hemorrhage was encountered nor was there any perforation of the viscera. The blood pressure was 140 systolic and 60 diastolic. Five hundred cubic centimeters of normal plasma was given to prevent shock; the specific gravities dropped to 1.055 (whole blood) and 1.025 (serum). During the subsequent thirty-two hours, 3,250 cc. of normal plasma and 3,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride, for reasons of dietary fluid intake, were administered. The specific gravities dropped to 1.046 (whole blood) and 1.025 (serum), but the patient progressed nicely.

Case 3.—A man was seen ten hours after injury, with a shrapnel perforation of the abdomen and peritoneal irritation. At laparotomy a small hematoma about the urinary bladder was found. There was no perforation of the viscera. Five hundred cubic centimeters of normal plasma and 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride were given, and the same fluids were repeated five hours later. Fifteen hours later the specific gravities were determined at 1.056 (whole blood) and 1.026 (serum). An additional 1,500 cc. of normal plasma and 2,000 cc. of dextrose in isotonic solution of sodium chloride were subsequently given. The urinary output was normal, and the progress of the patient continued satisfactorily.

Case 4.—A man was seen twelve hours after a laceration of the left thigh, near the inguinal region. No shock was apparent. The blood pressure was 130 systolic and 90 diastolic, the pulse was strong (rate 84) and the specific gravities were 1.055 (whole blood) and 1.026 (serum). No intravenous therapy was indicated, and the patient progressed satisfactorily on routine treatment.

2. Mild to moderate clinical signs of shock; normal or near normal specific gravity values.

Case 5.—A man was seen two hours after receiving multiple lacerations of the extremities. The clinical picture was satisfactory. The wounds were cleaned and dressed. Ten hours later the patient became restless and started sweating; the pulse became weak and the veins less prominent. He exhibited the clinical signs of shock. However, the specific gravities remained 1.051 (whole blood) and 1.025 (serum). One liter of normal plasma alleviated the signs; the blood pressure was 110 systolic and 62 diastolic and the specific gravities 1.046 (whole blood) and 1.025 (serum). Seven hours later the specific gravities were 1.043 (whole blood) and 1.025 (serum). Progress was satisfactory beyond this point.

Case 6.—A man was admitted to the hospital three hours following injury, with simple fracture of the left femur, with prominent swelling. The blood pressure was 130 systolic and 80 diastolic, and the specific gravities were 1.051 (whole blood) and 1.024 (serum), but the patient was pale and restless and his pulse was weak (rate 104). After 750 cc. of normal plasma, he became quiet and improved. The blood pressure was 120 systolic and 60 diastolic, and his pulse was stronger (rate 88). The fracture was set. Eighteen hours later the specific gravity was 1.046 (whole blood) and 1.0255 (serum), and the patient continued to do well.

3. Severe clinical shock, with normal or near normal values for specific gravity.

CASE 7.—A man with a fractured pelvis plus undetermined multiple injuries was seen eight hours after injury. He was in severe clinical shock (coma, imperceptible pulse, imperceptible veins and other symptoms). The specific gravity values were 1.055 (whole blood) and 1.025 (serum). He died before therapy could be started.

CASE 8.—A patient was observed four hours after injury consisting in fractures of the left tibia and right humerus. Signs of severe shock, including mild mental dulness, a weak, almost imperceptible pulse and pallor, were present. Specific gravity readings were 1.054 (whole blood) and 1.0255 (serum). He was given 300 cc. of a concentrated albumin solution (75 Gm. of albumin) and 1,200 cc. of citrated blood, after which he began talking rationally and complained of pain and his pulse became strong. His subsequent progress was good.

4. Severe shock with low values for specific gravity.

CASE 9.—A man was seen three hours after injury consisting in compound fractures of both legs (left tibia comminuted). Specific gravity of the blood was 1.041, and there was severe shock (imperceptible pulse, obscure veins and comatose state). During the ensuing seven hours, the patient was given 2,700 cc. of normal plasma and 1,800 cc. of citrated blood, this before and during operation (amputation of the left leg and application of a cast to the right lower extremity). Specific gravity values were 1.043 (blood) and 1.044 (serum). Shock was clinically controlled. After operation, 450 cc. of citrated blood and 250 cc. of normal plasma were given and the specific gravity of the blood was 1.042. After three hours (ten and one-half hours after admission) the specific gravity of the blood was 1.033. The patient was given 1,350 cc. of citrated blood and 1,300 cc. of 5 per cent dextrose in isotonic solution of sodium chloride during the next five and one-half hours (sixteen hours after admission), after which the specific gravities rose to 1.040 (whole blood) and 1.023 (serum). The following day (twenty-four hours after admission) the specific gravity readings were 1.035 (whole blood) and 1.0245 (serum), and at forty-eight hours the specific gravity of the blood was 1.041. Shock was controlled, but severe anemia persisted up to the time of his transfer. Two weeks later his progress was reported as good.

CASE 10.—A patient was observed about five hours after injury, with a comminuted compound fracture of the left tibia and fibula (the limb being fully crushed) and lacerations of the upper part of the right arm and the right leg. He was in severe shock, and specific gravities were 1.030 (whole blood) and 1.022 (serum). To cope with shock and prepare him for operation (amputation of the left leg), he was given 3,250 cc. of normal plasma and 2,400 cc. of citrated blood in 7.8 hours. During operation severe shock reappeared, as evidenced by pallor, imperceptible pulse, poor filling of veins and similar symptoms. The specific gravities now were 1.039 (whole blood) and 1.022 (serum), and 200 cc. of concentrated albumin solution (50 Gm. of albumin) was given rapidly, followed by immediate improvement. During the following two and one-half hours (ten and one-half hours after admission) an additional 2,675 cc. of citrated blood and 500 cc. of normal plasma were given (over-all total: 5,075 cc. of citrated blood, 3,750 cc. of normal plasma and 200 cc. of concentrated albumin solution). He was able to take fluids and food by mouth and subsequently progressed well.

Case 11.—A patient was first observed four and one-half hours after injury, with a severe compound fracture of the left humerus and lacerations of the right arm and scalp. He had received 750 cc. of normal plasma prior to arrival. Specific gravity readings were 1.048 (whole blood) and 1.025 (serum), and he showed evidences of severe shock, coma, imperceptible pulse, pronounced pallor and grayish blue mottling of the skin, inconspicuous veins, normal cutaneous turgor and other symptoms. He was given 500 cc. of concentrated albumin solution (125 Gm. of albumin) within the next fifty minutes, after which his veins filled and became more available for citrated blood, which was started. One hour after administration of the albumin solution, while the blood was being given, the specific gravity readings were 1.042 (whole blood) and 1.026 (serum) and another hour later 1.048 (whole blood) and 1.026 (serum). Altogether, 3,300 cc. of citrated blood was given within 6.8 hours of his admission. The arm was amputated during the latter part of the transfusions, about five hours after admission. He progressed well subsequently.

Case 12.—A patient was observed fourteen hours after injury, with extensive lacerations of the upper part of the left arm. The clinical picture was that of severe shock (weak pulse [rate 106], blood pressure 100 systolic and 64 diastolic, mental cloudiness and pale but dry skin). The specific gravities were 1.047 (whole blood) and 1.023 (serum). His history revealed that there had been no urinary output in eighteen hours; yet the bladder seemed empty. After twenty-five minutes of observation, his condition was unchanged; the values for specific gravity remained at 1.047 (whole blood) and 1.023 (serum). Following the administration of 1,200 cc. of citrated blood and 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride, the blood pressure was 116 systolic and 75 diastolic and the patient showed clinical improvement and subsequent normal urinary output. Four hours after infusions, the specific gravity readings were 1.047 (whole blood) and 1.023 (serum).

Case 13.—This report demonstrates transient hypertension in a hemorrhagic patient. He was seen three and one-half hours after injury causing extensive lacerations of the shoulder and compound fracture of the humerus. Five hundred cubic centimeters of normal plasma was given prior to his arrival. The specific gravities were 1.043 (whole blood) and 1.024 (serum), and he exhibited clinical signs of shock. He was given 1,000 cc. of citrated blood and 1,250 cc. of normal plasma, with clinical improvement to the pulse, which became strong (rate 96). The patient was mentally alert. The veins became easily accessible. During operation (débridement and other treatment) oozing of the blood occurred, the pulse rate was 108 and the blood pressure 160 systolic and 80 diastolic. During the next thirty minutes the blood pressure dropped rapidly; (120 systolic and 60 diastolic, 114 systolic and 70 diastolic and 100 systolic and 54 diastolic), the pulse became rapid (rate 150) and weak and other signs of shock appeared. The specific gravities were 1.040 (whole blood) and 1.025 (serum). After transfusion of 1,900 cc. of citrated blood and 600 cc. of normal plasma, signs of shock abated; later, specific gravity of the blood was 1.043. The patient was transferred before the posthemorrhagic anemia was properly treated, but satisfactory recovery was reported later.

Case 14.—Originally a patient was treated for shock with plasma in the field. When seen by us, he had severe anemia and went into shock at operation. He was seen twenty-four hours after injury, with compound fractures of the right tibia and fibula and lacerations about the left shoulder. He had received 1,750 cc. of plasma, shortly after injury, for "shock." On his arrival, the pulse rate

was 104, the oral temperature was 101.6 F. and he was extremely weak, but the veins filled well and there were no signs of shock. The specific gravity readings were 1.038 (whole blood) and 1.024 (serum), and the right foot was cold and blue beyond the cast; twenty minutes later the specific gravities were 1.037 (whole blood) and 1.024 (serum). During the next four and one-half hours, 2,000 cc. of citrated blood was given; the specific gravities eighteen hours after the blood was given were 1.0425 (whole blood) and 1.023 (serum) and eight hours later 1.042 (whole blood) and 1.023 (serum). Within the next 5.2 hours an additional 1,600 cc. of blood was given. Improvement continued.

Before operation (amputation of the lower third of the right thigh) and forty-five hours after admission, the specific gravities were 1.047 (whole blood) and 1.023 (serum), the blood pressure was 130 systolic and 80 diastolic and the pulse rate 116. There were no indications of shock. During operation the blood pressure dropped to 104 systolic and 56 diastolic and the pulse weakened; the specific gravities were 1.044 (whole blood) and 1.0215 (serum), and 300 cc. of concentrated albumin solution (75 Gm. of albumin) was given in fifty-five minutes. After this therapy the patient showed prompt improvement, the pulse became stronger (rate 100) and other signs of shock disappeared. Five and one-half hours later, the specific gravities were 1.040 (whole blood) and 1.023 (serum) and the blood pressure was 116 systolic and 66 diastolic. Administration of citrated blood was started. After 1,100 cc. of citrated blood, he showed additional improvement, with the blood pressure 128 systolic and 80 diastolic and a pulse rate of 90. Fifteen hours later the specific gravities were 1.0425 (whole blood) and 1.023 (serum), the blood pressure was 124 systolic and 78 diastolic, the pulse rate 88 and the oral temperature 99.6 F. Five and one-half hours later the specific gravities were 1.0445 (whole blood) and 1.023 (serum). During the subsequent twenty-four hours, 400 cc. of concentrated plasma (threefold) and 300 cc. of concentrated albumin solution (75 Gm of albumin) were given for hypoproteinemia. The patient was progressing well at transfer, seventy-two hours after admission.

Case 15.—A patient was seen thirty minutes after injury, with a shrapnel perforation of the chest posteriorly. He was pale and gasping slightly. His veins were filled fairly well, the pulse was weak (rate 120) and the blood pressure was 88 systolic, by palpatory technic. He was observed thirty minutes later, during which time the signs were unchanged. The blood pressure was 78 systolic, and the specific gravities were 1.046 (whole blood) and 1.022 (serum). During the next two hours 1,500 cc. of normal plasma was given, with clinical improvement. The blood pressure was 108 systolic, the pulse rate was 120 and the specific gravities were 1.044 (whole blood) and 1.025 (serum). Then 2,000 cc. of citrated blood was given in the next four hours, with pronounced improvement (lips pink and pulse strong [rate 110]), the blood pressure was 120 systolic and 70 diastolic and the specific gravities were 1.046 (whole blood) and 1.025 (serum). Twenty-four hours later he was resting quietly and could ingest liquid nourishment, and the specific gravities were 1.047 (whole blood) and 1.025 (serum). The final diagnosis was shrapnel perforation of the chest, with hemothorax.

B. Patients Seen Thirty-Six to Forty-Eight Hours After Injury, When Anemia and Hypoproteinemia Were Prominent:

Case 16.—A patient was admitted seven days after an injury causing compound fractures of both tibias and fibulas; the cast was permeated with dried blood. The patient had received 2,000 cc. of normal plasma shortly after the

injury. The specific gravities on arrival were 1.032 (whole blood) and 1.023 (serum). The patient was extremely weak, badly confused mentally and at times semidelirious. A check of the specific gravities two hours later, when administration of blood was started, gave 1.033 (whole blood) and 1.023 (serum). During the next fourteen hours he was given 3,360 cc. of citrated blood (after 2,000 cc. the specific gravities rose to 1.045 [whole blood] and 1.023 [serum]), and four hours after the administration of blood the specific gravities were 1.054 (whole blood) and 1.025 (serum). Clinical improvement was outstanding. The patient demanded food, was able to ingest a light diet and showed further satisfactory progress.

CASE 17.—A patient was injured twenty-seven days before admission. He had a perforation of the abdomen, requiring colostomy, and had received a transfusion of 1,500 cc. of blood. He was emaciated and on a starvation diet, with specific gravity readings of 1.046 (whole blood) and 1.016 (serum). He showed pronounced restlessness and had insomnia. Specific gravity readings were partly masked by the chronic dehydration. Two thousand four hundred cubic centimeters of citrated blood was given while the patient was observed closely. He received also 100 mg. of thiamine hydrochloride and 200 mg. of ascorbic acid. He slept well that night and appeared much stronger at the time that he was transferred.

CASE 18.—A patient had sustained a fracture of the left forearm forty-eight hours before admission; 250 cc. of normal plasma had been given. On admission he had evidences of gas gangrene (oral temperature was 104 F., and pulse rate was 132) and specific gravities were 1.0405 (whole blood) and 1.023 (serum). The administration of blood was started and amputation performed. He was given 3,000 cc. of citrated blood in six hours. Four hours after the blood was given, the specific gravity readings were 1.047 (whole blood) and 1.023 (serum). During the next twenty-four hours the patient was given 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride, 750 cc. of normal plasma and 400 cc. of concentrated plasma (fourfold) for dietary hypoproteinemia. He was recovering satisfactorily when transferred.

CASE 19.—A patient was seen nine days after injury causing multiple shrapnel lacerations of the buttocks and thighs. Specific gravities were 1.046 (whole blood) and 1.0245 (serum). Clinically he was pale, but there were no alarming signs of shock. He was given 3,600 cc. of citrated blood during the next twenty-four hours, and twenty-four hours later the specific gravity readings were 1.056 (whole blood) and 1.025 (serum). The intake-output of water was normal, the urine was normal and the patient was recovering nicely when transferred.

The manner in which the red cell concentration (specific gravity) of the blood reached its peak after transfusion is demonstrated in 2 cases:

CASE 20.—A patient was seen three hours after injury causing perineal lacerations and damage to the urethra. Hemorrhage was still in progress when he was admitted. The specific gravities were 1.051 (whole blood) and 1.024 (serum). There were no definite signs of shock (compensation was adequate). The blood pressure was 140 systolic and 80 diastolic, and the pulse rate was 120. There was definite pallor, and the veins were less prominent. Before and during operative repair, 1,800 cc. of citrated blood was given; in six hours the specific gravities were 1.055 (whole blood) and 1.025 (serum), two hours later they were 1.055-

(whole blood) and 1.0255 (serum) and eleven hours later (nineteen hours after admission) they were 1.057 (whole blood) and 1.027 (serum). The patient remained well hydrated during these periods.

CASE 21.—A patient showed a greater hemodilution originally. He was seen forty-eight hours after injury necessitating amputation of the left leg below the knee. The blood pressure was 140 systolic and 70 diastolic, the pulse rate was 100 and the specific gravities were 1.037 (whole blood) and 1.020 (serum). Within three and one-half hours, 2,400 cc. of citrated blood was given; eight and one-half hours later the specific gravities were 1.045 (whole blood) and 1.022 (serum) and twenty-four hours beyond this 1.048 (whole blood) and 1.0235 (serum). The patient kept well hydrated. Despite substantial transfusion, it was not sufficient to cope with the anemia completely.

A paradoxic change in the values for specific gravity was observed in rare cases in which the patients did not display evidence of hemolysis. In these instances, a substantial transfusion was followed by prominent hemodilution.

CASE 22.—A patient was seen 2.8 hours after injury causing multiple lacerations. Clinical shock was prominent; specific gravities were 1.050 (whole blood) and 1.025 (serum). Within eight hours he was given 3,000 cc. of citrated blood and 500 cc. of normal plasma, and six hours later the specific gravities were 1.046 (whole blood) and 1.022 (serum). Shock was controlled. The explanation for this is that extreme depletion of blood volume had occurred, which was only partly replenished even with a substantial transfusion. Compensatory mechanisms reflected a clinical recovery after the volume was partly replenished. Hemodilution resulted.

II. *Plasmorrhagic Group.*—A. Normal or Near Normal Clinical Picture and Normal or Near Normal Specific Gravity Values:

The patients in the plasmorrhagic group had superficial though frequently widespread burns, with no visible swelling and no particular alterations in the values for specific gravity, and a normal clinical picture. Mild or no therapy was followed by a satisfactory clinical course.

CASE 1.—A patient was seen about thirty hours after receiving burns of the face, upper extremities, hands and back. All burns were superficial. There had been no previous therapy. Specific gravities were 1.057 (whole blood) and 1.026 (serum). No intravenous therapy was given. His progress was good.

CASE 2.—A patient was seen about thirty hours after receiving a burn. There had been no previous therapy. Burns of the face, neck and both legs and hands were superficial. Specific gravities were 1.056 (whole blood) and 1.0245 (serum). He was given 750 cc. of normal plasma but no other therapy. His progress was good.

CASE 3.—A patient was seen three hours after receiving burns of the face, neck, upper extremities and a small part of the chest anteriorly. No shock was present. The specific gravities were 1.056 (whole blood) and 1.027 (serum). He was given 500 cc. of normal plasma but no other therapy. His progress was good.

CASE 4.—A patient was seen eighteen hours after receiving burns of the arms, hands and face. There was no shock. Specific gravities were 1.0575 (whole blood) and 1.023 (serum). He was given 500 cc. of normal plasma and 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. Thirteen hours later the specific gravities were 1.054 (whole blood) and 1.023 (serum). His progress was good.

B. Case of Severe Hemoconcentration: Early and later period. The period of shock and the subsequent period of anemia and hypoproteinemia are illustrated in this report of a case of a severely burned patient treated for ten days and followed subsequently.

H. B. was burned in an explosion aboard a landing craft. The heat was intense enough to burn all the clothing off his body, leaving all body surfaces burned except the area covered by trunks (see fig. 1). By Berkow's classification[7] 80 per cent of the body surface was involved. The patient was seen two hours after the burn, when specific gravity readings were taken and treatment started.

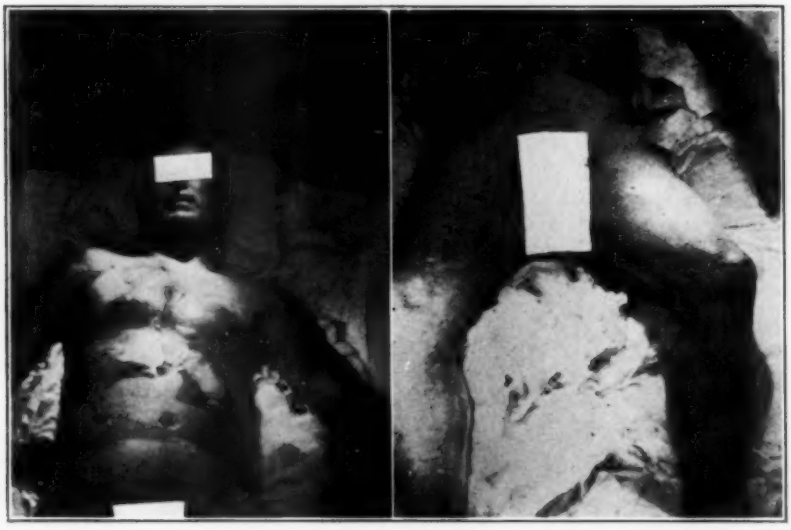


Fig. 1.—These figures indicate the extent of body surface burned on H. B. The exposures were taken during the latter part of the stay, when much of the swelling had subsided. The burns of the back corresponded to these anterior zones, the prominent lines of demarcation at lower trunk and upper thigh continuing on around. Swelling of the face and neck had completely subsided. (Dr. Herbert Alden, Atlanta, Ga., supplied this photograph.)

Figure 2 shows changes in specific gravity over a period of ten days and after fluids had been given intravenously. Notice the 5,200 cc. of normal plasma (about 300 Gm. of proteins) and 585 cc. of concentrated albumin solution (146 Gm. of albumin) during the first forty-eight hours to control hemoconcentration,

7. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. **8**:138-148 (Jan.) 1924.

80 per cent of which was given during the first twenty-four hours. When values for specific gravity began dropping, they continued to do so despite the administration of 2,600 cc. of citrated blood; the lowest levels, 1.049 (whole blood) and 1.0225 (serum), occurred after transfusions. Oral intake, of the amount desired, during this time was 2,400 to 3,200 cc. in twenty-four hours, and the urinary output was 1,600 to 2,800 cc. per twenty-four hours. During the last seventy-two hours, values for specific gravity returned to normal and oral intake and urinary output doubled, 6,800 to 8,200 cc. and 4,000 to 5,000 cc. respectively.

The patient's injuries consisted of massive burns, mostly second degree, with extreme swelling despite moderate compression dressings. Usual high remittent temperature (oral temperature 101 to 103 F.) during the first four days lowered to 99 to 100 F. during the last days. Penicillin (20,000 Oxford units every three hours) was given intravenously and intramuscularly throughout. Locally unmedicated white petrolatum gauze, with moderate compression dressings, was used.

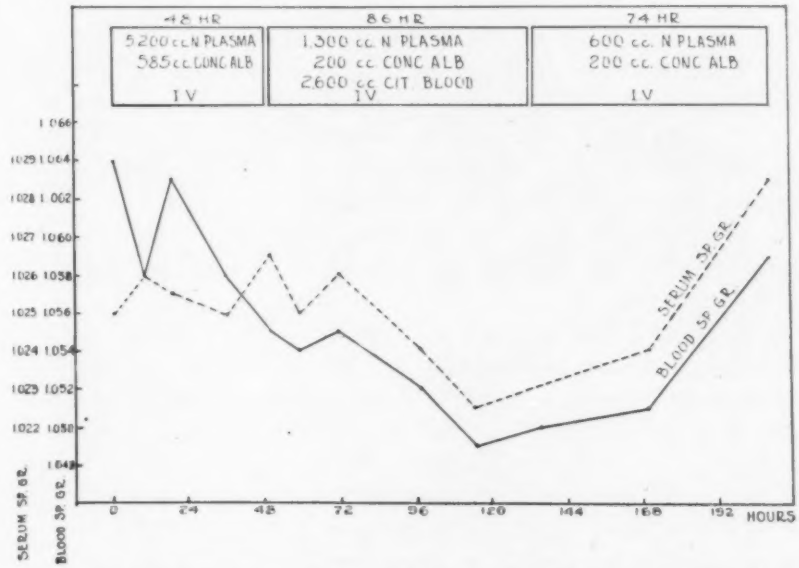


Fig. 2.—The specific gravity values for blood serum over a nine day period for H. B., a patient in a case of burn, are given together with the fluids administered intravenously and the intervals when these were given. The patient had an 80 per cent body surface burn and recovered.

The patient was allowed free access to fluids taken orally, and thiamine hydrochloride (25 to 75 mg.) and ascorbic acid (50 to 200 mg.) were given daily parenterally.

With close attention given to oral dietary intake, after seventy-two hours it was possible to give the patient 150 to 200 Gm. of proteins by mouth, in the form of albumin—eggs, milk, cheese and meats. Carbohydrate intake was maintained without difficulty.

Mild mental confusion and irrelevant soliloquies appeared periodically during the early phase, especially the first seventy-two hours, but at all times the patient was mentally accessible and cooperative. Swelling of the face and neck was pronounced during the first forty-eight hours in areas where no compression

dressing was used. Swelling began to disappear after sixty to seventy-two hours but still was noticeable after seventy-two hours (see fig. 1).

Infection (demonstrated by usual yellowish green exudate) was limited to scattered areas. Two months later the patient was convalescing and progressing well.

COMMENT

For both hemorrhagic (lacerations and fractures) and plasmorrhagic (burns) patients, the term "shock" is used to cover the clinical signs indicative of oligemia. Prominent among these signs are a weak pulse, pallor, sweating, coldness of the skin, inconspicuous superficial veins, ashen cyanosis and lowered blood pressure. In the cases of severer injury, mental cloudiness, restlessness or coma and oliguria were present. Compensatory mechanisms at times obscured some of these signs.

It is understood that certain fundamental differences in the pathogenesis of the two types of oligemia exist,[8] outstanding being hemodilution in hemorrhagic patients and hemoconcentration in patients with burns; yet, from the clinical view the proper treatment of the oligemia during the therapeutically amenable period, usually the early hours, ameliorated the similar signs in the two types.

The application of the four mentioned criteria afforded the best means of judging the oligemic needs for fluids during the period of shock in both types.

The extent and type of injury not only naturally segregated the two major types, i. e., the hemorrhagic and plasmorrhagic, but also was indicative of the severity of existing or potentially developing oligemia. In isolated instances a small laceration strategically placed (such as a small laceration severing the brachial artery) initiated copious hemorrhages, but in the great majority the extent of the injury paralelled the extent of blood loss. Thus, an analysis of the types and extent of injury considering the greater to the lesser degree of blood loss gave a list somewhat as follows: multiple compound fractures (especially comminuted type), single compound fracture, severe abdominal injury, severe thoracic injury, multiple lacerations, simple fracture and single laceration.

For cases of burns the extent of body surface involved was not so important as the depth of swelling of burned sites. It was, therefore, considered precarious to judge needs for protein and salt during the oligemic period by the percentage of body surface involved alone. For instance, many patients (following *kamikaze* attacks) with extensive superficial burns and little or no visible swelling had no particular elevation of specific gravity and required little or no intravenous ther-

8. Moon, V. H.: Shock: Its Dynamics, Occurrence and Management, Philadelphia, Lea & Febiger, 1942.

apy. Conversely, a patient with a partial burn of one upper extremity and much swelling had severe concentration (specific gravities 1.067 [whole blood] and 1.026 [serum]) and required 400 cc. of concentrated albumin solution and 1,000 cc. of normal plasma to lower specific gravity values to 1.052 (whole blood) and 1.025 (serum). These observations were made in the types of cases discussed by British workers.[9]

The one outstanding variable in evaluating the clinical signs of shocks (clinical picture) was the level at which compensatory mechanisms came into play. This problem may be elucidated as follows: Minor grades of deficit (the donor parting with 500 cc.) are attended by minor or no signs of shock.[10] It is usually considered that losses of 1,000 cc. are frequently well tolerated, though a few signs of mild shock may appear (transient weakness, giddiness, fatigue, slight tachycardia, slight sweating and other signs). Beyond 1 liter, compensatory mechanisms are apt to break down.[11] Physiologists have emphasized that a 30 per cent acute blood loss (1,500 to 2,500 cc. in average persons) is followed by prominent decompensation and signs of shock.[12] The reverse of these considerations also appears practical. Thus, as therapy is given, a point is reached when compensatory mechanisms come into play and obscure clinical signs, yet complete replacement may not have occurred.[13] Persistent hemodilution and persistent hemoconcentration demonstrate deficits subsequently. In this series of patients, those who failed to exhibit any outstanding change from normal in the criteria used progressed satisfactorily.

The main patterns observed in the hemorrhagic patients can be classified in four types. First, there are the patients seen in early hours following the injury with a simple fracture of the femur or humerus or lacerations, displaying mild to moderate clinical signs of shock and normal or slightly lowered specific gravity values of blood and serum. Concentrated albumin solution (150 to 300 cc.), concentrated plasma (150 to 300 cc.) or normal plasma (700 to 1,500 cc.) given to these

9. Colebrook, L., and others: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43), reviewed, J. A. M. A. **128**: 907-908 (July 21) 1945.

10. Boynton, M. H., and Taylor, E. S.: Complications Arising in Donors in Mass Blood Procurement Project, Am. J. M. Sc. **209**:421-436 (April) 1945.

11. McMichael, J.: Clinical Aspects of Shock, J. A. M. A. **124**:275-281 (Jan. 29) 1944.

12. Macleod, J. J. R.: Macleod's Physiology in Modern Medicine, edited by P. Bard, ed. 9, St. Louis, C. V. Mosby Company, 1941, pp. 518-521.

13. For instance, Magladery, Solandt and Best in an experimental study observed that a 40 per cent replacement in hemorrhages effected recovery. Magladery, J. W.; Solandt, D. Y., and Best, C. H.: Serum and Plasma in Treatment of Haemorrhage in Experimental Animals, Brit. M. J. **2**:248-250 (Aug. 24) 1940.

patients diminishes the clinical signs of shock, and the specific gravity of the blood drops below normal limits. Many such patients continue on the road to recovery, manufacturing their own red cells for replacement, especially if the injuries are uncomplicated by infection or starvation. Second, there are similar patients, whose specific gravities continue to drop to lower levels (1.044 [whole blood] and 1.024 [serum]). Blood transfusions are helpful here but may not be absolutely required unless other complications exist. However, one would not hesitate in giving blood to these patients if it is readily available. Third, there are the patients with compound fractures and/or multiple lacerations, exhibiting pronounced signs of shock. The patients require greater quantities of protein solutions (400 to 500 cc. of concentrated albumin or 2,000 cc. of normal plasma). The specific gravity of the blood drops rapidly to 1.040 or lower, and at this point blood transfusion (1,200 to 3,000 cc.) are required. In most of these patients, when blood is not given severe anemia develops. Fourth, patients with severe injuries, as comminuted fractures or mangled extremities, severe abdominal wounds or thoracic wounds, clinical signs of severe shock (coma, imperceptible pulse and veins, low blood pressure, pallor and other symptoms) and specific gravity values lowered, though the injury has recently occurred, or specific gravities of the blood that drop rapidly after protein solutions, require heroic measures. Three hundred to 600 cc. of concentrated protein solutions and 2,400 to 3,500 cc. of citrated blood give the best results. The volume depletion in these cases was frequently amazing, and so long as the criteria used indicated a favorable trend and venous engorgement and pulmonary rales did not develop the administration of these two fluids (or similar types) was continued. The excellent results obtained in treating these severely injured and moribund casualties justified the procedure used.

The main criterion used as a therapeutic guide for cases of burns during the shock period was the specific gravity value of blood and serum. An attempt was made at all times to control hemoconcentration, regardless of the volumes of concentrated and normal protein-salt solutions required. This technic appeared successful even in cases of severe injury.

Usually, concentrated albumin solution and normal plasma were given rapidly to the patients with burns until the specific gravity of the blood or hemoglobin concentration became normal (for specific gravity around 1.058). The infusion was then continued slowly for one hour and the specific gravity rechecked. When hemoconcentration reappeared, additional protein-salt was given. This process was continued until hemoconcentration failed to develop. The main bulk of protein solution was always given the first twenty-four hours. After forty-eight

to seventy-two hours, the period of anemia and hypoproteinemia appeared.

Following the period of shock there were four primary conditions which were at all times considered: (1) developing anemia, (2) hypoproteinemia, (3) maintenance of adequate water-salt intake and urinary output and (4) food supplements (protein, carbohydrate and vitamins) by vein to supply metabolic needs and prevent body wastage.

Anemia was at times severe. In such cases larger transfusions seemed beneficial and were given, without circulatory volume complications. Hypoproteinemia seemed controlled better when treated at the same time as the anemia.

CONCLUSIONS

1. Of 5,000 battle casualties handled by a front line medical activity, 345 were closely observed and especially studied for needs for parenteral administration of fluid. The application of four criteria (clinical picture, blood pressure, specific gravities of blood and serum and the response to therapy) seemed to afford the best means of judging these needs.

2. All patients could be divided into two groups: (1) those with loss of blood (hemorrhagic) and (2) those with loss of plasma (plasmorrhagic).

Group 1 included patients with fractures, various lacerations and practically all types of battle injuries. Group 2 included patients with burns.

3. Patients in both groups subsequently tended to display anemia and hypoproteinemia, particularly (1) when insufficiently treated early with the proper fluids given parenterally, (2) when infections developed or (3) when on a starvation diet.

4. The criteria were particularly useful during the earlier hours following the injury, when "shock" was more apt to occur. In both groups "shock" was used as a means of identifying oligemia (blood loss oligemia and plasma loss oligemia) and was considered to exist when well known signs persisted. The main signs used were a weak pulse, inconspicuous superficial veins, cyanosis and lowered blood pressure, coldness, pallor, sweating, mental signs, oliguria and deviation from normal specific gravity values for blood and serum.

5. The proper replenishment of the blood volume, as judged by the improvement in the criteria mentioned, nullified the signs of shock in both groups.

6. Citrated blood was an essential fluid for both groups and was indispensable for the hemorrhagic patients. Concentrated protein solutions (albumin and plasma) were most effective in coping with oligemia so long as the cutaneous turgor was normal or near normal. These con-

centrated solutions were of particular value in the severer grade of shock and in burns.

7. The specific gravity values determined by the copper sulfate method were extremely useful and most practical for a quick and dependable therapeutic guide.

8. Frequently, large infusions (what have been termed massive) were required to cope with the fluid losses. It was clearly observed that in cases in which the need was great the larger volumes were not just beneficial but essential. Venous engorgement and pulmonary rales, the outstanding signs of a circulatory overload, were not observed in these patients. This is probably due to the fact that all casualties treated had suffered severe fluid losses and the massive infusions and transfusions were replacements for those fluid losses.

9. During the period beyond the shock interval, the use of the specific gravity values and the application of established principles (dietary intake, urinary output, clinical response to treatment and other factors) became more important in the decision on needs for fluid. More elaborate procedures were not available.

10. The copper sulfate specific gravity method for determining the hemoglobin concentration and plasma protein values was of inestimable value in the proper treatment of battle casualties. The method is so simple that it can be used under combat conditions, and when added to the clinical observations noted as criteria for evaluating shock, fluid therapy and dietary requirements provides much of the data necessary for the intelligent handling of casualties in the early phases of a military operation, when more elaborate facilities are not available.

PULSATING BENIGN GIANT CELL TUMORS OF BONE

Report of a Case and Review of the Literature

THOMAS A. SHALLOW, M.D.
AND
FREDERICK B. WAGNER Jr., M.D.
PHILADELPHIA

PULSATING tumors of bone present unusual difficulties both in differential diagnosis and in treatment. This applies particularly to the so-called pulsating benign giant cell tumor because of its resemblance to highly malignant tumors and its constant threat of malignant transformation. The surprisingly few reported cases warrant the accumulation of all the available data in order to obtain more information concerning the nature of this lesion and its proper treatment. For this reason, an additional case is reported in detail and the literature is reviewed.

REPORT OF A CASE

M. S., a white youth aged 20, was admitted to the surgical "A" service of the Jefferson Medical College Hospital Aug. 12, 1942, with the chief complaint of a lump just below the left knee.

In April 1942, while working, the patient sprained his left ankle but received no injury to the knee. The pain disappeared after one month, after treatment by strapping and infra-red light. About two weeks after the injury to the ankle, however, he experienced a dull, nagging, constant ache at the upper end of the left tibia. This was not severe enough to cause loss of sleep. The discomfort persisted until July 1942, at which time he noticed one day that his leg was extremely and diffusely swollen from the knee down to the ankle. This condition was treated with rest in bed and hot compresses for one week, after which the diffuse swelling and pain subsided, but a hard, nontender lump persisted on the anterolateral aspect of the leg, just below the knee. This remained essentially the same size until the patient was admitted to the hospital. There was no loss of weight, and his general health was otherwise excellent.

The past medical history was uneventful, and the family history failed to reveal any member's ever suffering from similar complaints.

Physical Examination.—The patient was a well developed, well nourished Jewish youth. The significant physical findings were confined to the left lower extremity. A mass about 7 by 5 cm. was visible on the anterolateral aspect of the upper end of the left tibia. The mass was hard, nodular and nontender and was fixed to the underlying bone. It was not sharply demarcated, and the overlying skin was freely movable. No pulsation was felt at this time. There was slight enlargement of the inguinal lymph nodes bilaterally.

From the Samuel D. Gross Surgical Division of the Jefferson Medical College Hospital.

Laboratory Data.—The blood count revealed the hemoglobin to be 88 per cent, red cells 4,160,000 and white cells 8,000, and the differential count was normal. Results of repeated urine tests were normal. The blood Wassermann and Kahn reactions were negative. The serum calcium was 11 mg., phosphorus 4.4 mg. and phosphatase 1.4 Bodansky units. Roentgen ray examination of the left tibia revealed the presence of a typical benign giant cell tumor at the proximal extremity (fig. 1 *A*). The other long bones, spine, pelvis and chest were normal.

It was the opinion of the radiology department that in this case surgical intervention was preferable to roentgen therapy. Accordingly, operation was performed, with the patient under spinal anesthesia, on August 24.

Operation.—The left lower extremity was prepared and a tourniquet applied loosely around the thigh, to be tightened if necessary to control bleeding. A longitudinal incision 3 inches (7.6 cm.) in length was made over the anterolateral aspect of the mass. The anterior wall of bone, which was no more than

Fig. 1.—Roentgenograms showing benign giant cell tumor at proximal extremity of left tibia. In *A*, the lesion is shown preoperatively. The corresponding view of the right tibia is normal. In *B*, the lesion twenty-two months postoperatively shows an increase in extent despite surgical and radiation therapy.

3/16 inch (.48 cm.) thick, was chiseled away. The underlying tumor consisted of dark brown gelatinous material and was seen to pulsate vigorously with each heart beat. Curettement was performed, accompanied with much troublesome bleeding, which required tightening of the tourniquet from time to time for control. Posteriorly, in which area the tumor was in close relationship with the popliteal artery, there was no bony shell. At this site pronounced bleeding was suddenly encountered, and it could be controlled only by the tightening of the tourniquet. For this reason, further curettement had to be abandoned and the advisability of amputation above the knee was considered. A decision was made to attempt to save the limb, and, with the tourniquet still applied, 8 Gm. of sulfanilamide were placed in the cavity, which was packed tightly with iodo-

form gauze. The cavity had a capacity of about 80 cc. On release of the tourniquet, no further bleeding was encountered. A plaster posterior molded splint was applied to the extremity. The patient left the operating room in good condition, with the tourniquet applied loosely around the thigh, in readiness to be tightened should severe bleeding be encountered subsequently.

Pathologic Report.—The pathologic report was benign giant cell tumor of the bone (fig. 6 *A*).

Postoperative Course.—The immediate convalescence was uneventful except for anemia (hemoglobin 65 per cent and red cells 3,500,000), which was treated by multiple blood transfusions and ferrous sulfate. Sulfadiazine was administered until the sixteenth day, with a blood level maintained between 5 and 8 mg. On the seventh day the pack was removed in the operating room with the patient under spinal anesthesia, because of the danger of further hemorrhage. Sulfanilamide crystals (8 Gm.) were placed in the cavity, and the wound was again packed with iodoform gauze. Subsequently the wound was treated with sulfanilamide irrigations and iodoform packs. At no time did the wound become infected. Roentgen ray examination on the thirty-fourth day revealed that curettement had been incomplete, and deep roentgen therapy was advised by the radiology department. This was started on the forty-second day, and a total of 2,024 r was given to the anterior and posterior fields over a period of eleven days. Serial roentgenograms showed a gradual filling in of the bony defect, but extensive mottling of the lateral portion of the head of the tibia persisted, strongly suggesting residual giant cell tumor. The patient was discharged to the care of his family physician on Jan. 30, 1943, five months and six days after operation. At this time there was still a cavity in the wound, with a volume of about 20 cc. A caliper brace was prescribed by the orthopedic department, permitting walking without weight bearing on the knee.

Second Admission.—The patient was referred for readmission by his family physician on March 9, 1943, because of excessive bleeding and pulsation of the wound noted during the preceding two weeks. Blood count, urine, serum calcium, phosphorus and phosphatase were normal. Roentgen ray examination revealed no significant changes in the appearance of the tumor area. The remainder of the bony skeleton and the lung fields were normal. A second course of roentgen therapy, consisting in 2,131 r, was given to anterior and posterior fields over a period of ten days, following which the wound healed and the pulsation ceased. The patient was discharged on April 3, 1943, to the further care of his family physician and to the follow-up care of the tumor clinic. Use of the walking caliper was continued.

Third Admission.—The patient was referred for readmission by the tumor clinic on June 12, 1944, because of roentgen ray evidence that the tumor was again increasing in size. His general health had remained excellent, there was no loss of weight and walking had been satisfactory with the aid of the caliper brace.

Physical examination revealed a mass about 2 cm. in diameter in the operative scar, near its upper pole (fig. 2). The mass was nontender, smooth, semifluctuant and adherent to the overlying skin, which was atrophic and of a purplish color. It had an expansile pulsation, a slight thrill and a soft systolic bruit, all of which could be abolished by compression of the femoral artery in the groin. The bruit was audible around the entire circumference of the leg, just below the knee, but was most noticeable anteriorly, in the area of the scar, and also posteri-

orly, over the popliteal vessels. The dorsalis pedis and posterior tibial pulses were easily felt and equal on both sides. The oscillometric readings were normal for the legs and feet. Aspiration of the mass in the scar readily yielded 5 cc. of blood, which clotted promptly.

The blood count and blood chemistry studies again gave normal results. Roentgen ray examination revealed that the tumor had again increased somewhat in size since the previous examination (fig. 1 *B*). Roentgenograms of the pelvis, spine, skull and chest showed no evidence of metastatic lesions.

Because of the unusual physical findings already described, it was thought that a false aneurysm might have resulted from the trauma of the first operation or

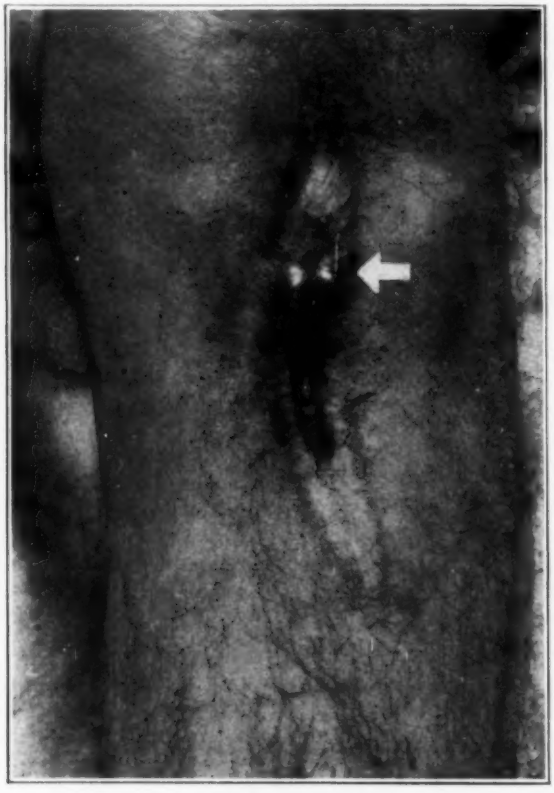


Fig. 2.—Expansile pulsating mass, indicated by arrow, in the scar twenty-two months following operation.

that there might possibly have been transformation into a malignant bone aneurysm. Arteriography, diodrast being used as contrast material, revealed the presence of many new, smaller vessels around the area of the tumor but no evidence of aneurysm (fig. 3). Venography revealed a normal venous circulation, with a well visualized deep vein running in the popliteal space (fig. 4). Few venous channels were seen in the tumor. Biopsy of one of the left inguinal nodes revealed no evidence of tumor involvement.

A third course of deep roentgen therapy, consisting of 1,000 r spread out over a period of twelve days, was administered to the anterior and posterior fields. The total dose of the three series was 5,155 r (200 kilovolts, 0.5 mm. of copper and 1 mm. of aluminum).

Because the lesion was progressing despite both surgical and roentgen ray therapy and because of the pronounced vascularity associated with physical signs of bone aneurysm, suggesting the possibility of malignant transformation, either potential or actual, it was deemed advisable to amputate above the knee. Conse-

Fig. 3.—Arteriogram showing many new smaller vessels around the area of the tumor.

quently, midthigh amputation with the patient under spinal anesthesia, was performed June 28, 1944.

Convalescence was uneventful, and the patient was discharged as well on July 31.

Pathologic Examination (by Dr. Peter A. Herbut).—Gross Examination: The specimen is a left lower extremity that has been amputated

in the middle third of the thigh. Approximately 5 cm. below the knee, there is an anteriorly placed, well healed, old operative incision. This extends for approximately 7.5 cm. distally. At this place and laterally, there is a fluctuant soft tissue mass that produces slight bulging of the cutaneous surfaces. Just beneath the previous incision of the skin there is a small area, measuring 2.5 by 2 cm., where soft, dark, beefy red

Fig. 4.—Venogram showing patency of the deep veins in the area of the tumor.

tumor tissue has broken through the deep fascia (fig. 5 *a*). The skin has not been penetrated. Dissection of the soft parts elsewhere reveals tumor tissue bulging from the head of the tibia into the surrounding muscle and fascia. The tumor tissue is limited by the overlying deep fascia. Posteriorly, a small mass of red and gray tumor tissue, measuring 2.5 by 3 cm., bulges out into the joint space between the tibial condyles (fig. 5 *b*). The cartilaginous surfaces are smooth and have

not been eroded. A coronal hemisection of the tumor mass and tibia reveals a tumor mass arising from the head of the tibia (fig. 5 *c*). Nearly the entire head of the tibia is replaced with soft, fleshy, tumor tissue. The surfaces are mottled—dark red, reddish gray and yellowish gray. The central portion is especially soft and hemorrhagic. The entire tumor mass measures 8 by 6 by 6 cm. in greatest diameters. Superiorly, tumor tissue lies immediately beneath the cortical bony layer of the knee joint. Both laterally and posteriorly the tumor has broken through and completely destroyed the cortical bone. Here, as previously described, tumor tissue is invading the surrounding musculature and soft tissues (fig. 5 *d*). Both medially and anteriorly the cortex of the tibia is intact, and 1.5 to 2 cm. of cancellous bone has not been invaded. Dissection

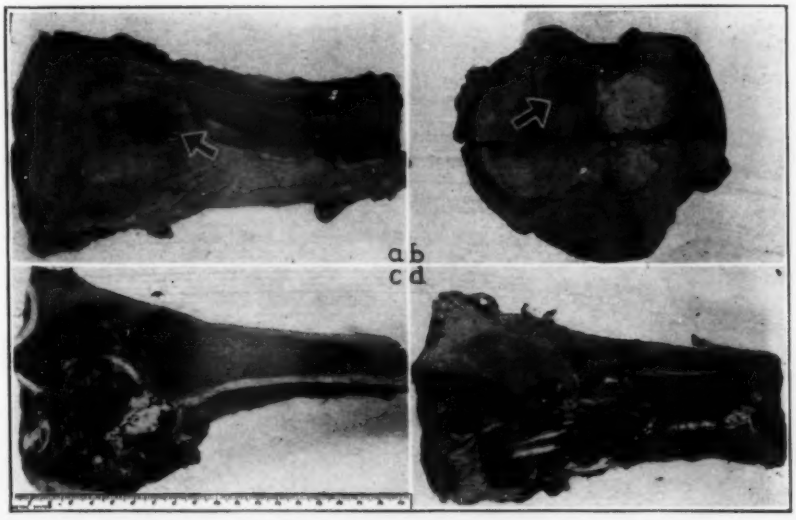
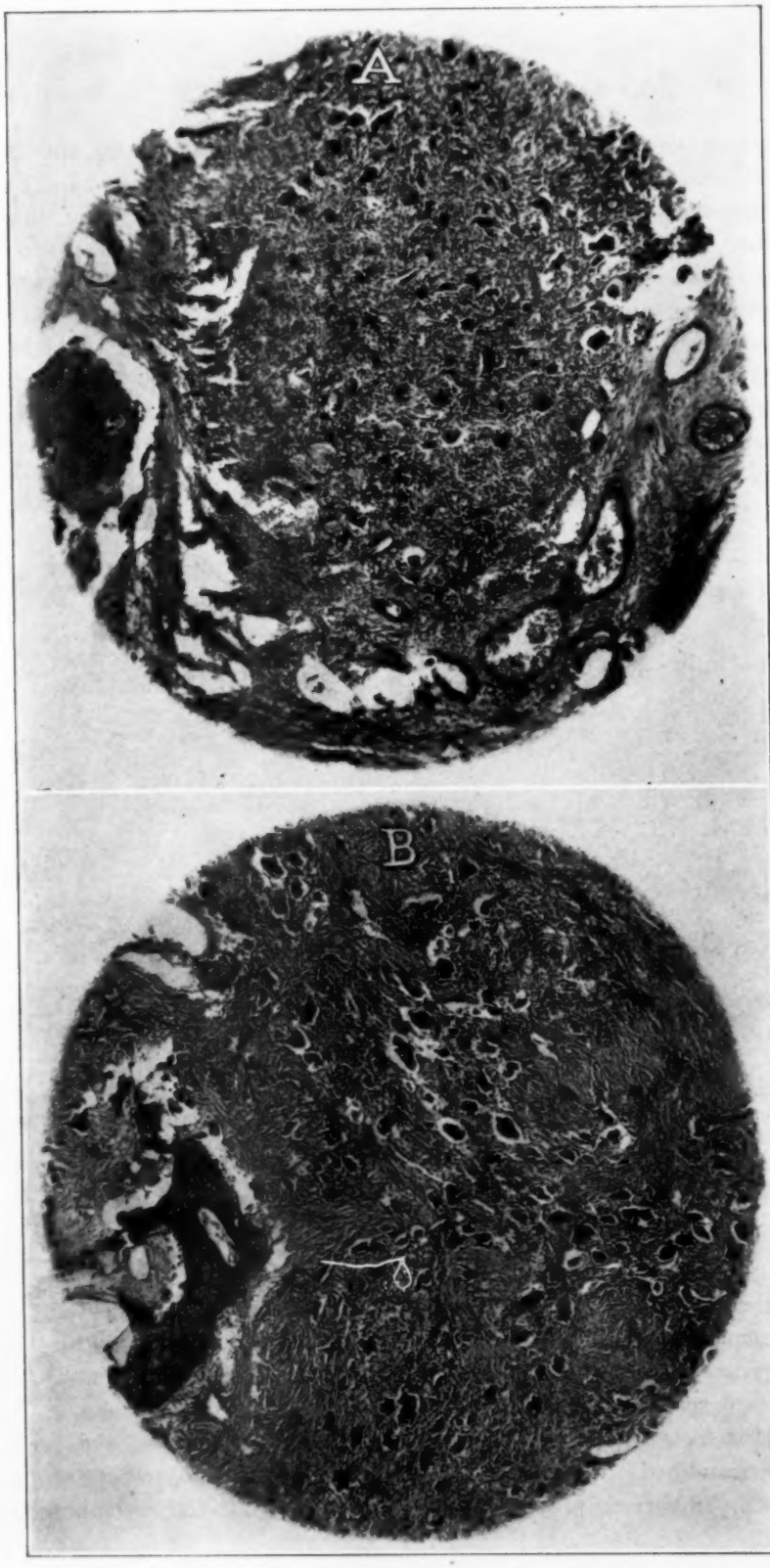


Fig. 5.—Gross specimen: (*a*) protrusion of tumor, indicated by arrow, anteriorly through deep fascia in area corresponding to figure 2; (*b*) tumor tissue, indicated by arrow, between the tibial condyles posteriorly; (*c*) coronal hemisection of proximal end of tibia, showing replacement of most of head by tumor; (*d*) posterior aspect, showing invasion of surrounding musculature.

of the popliteal, posterior tibial and peroneal arteries reveals no large vascular connections with the tumor mass. The vessels posteriorly lie on the deep fascia covering the tumor. There are no aneurysms or vascular anomalies. Further dissection of the tibial shaft reveals that the tumor is limited to the head and upper 3 cm. of the shaft. In the popliteal space there are two discrete reddish gray lymph nodes.

Histologic Examination: More than forty sections of the tumor were examined. They are all essentially similar and consist of two elements in varying proportions (fig. 6 *B*). The stroma is composed of



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connective tissue which in most sections is rather loose and cellular. The cells are relatively large. Their cytoplasm is abundant and elongated, but the borders are not sharp and they often blend with adjacent cells. The nuclei are mostly oblong or spindle shaped. Only occasionally are they round. They are, however, regular and evenly stained and show no hyperchromatism or mitosis. In other sections, there is a gradation from this cellular connective tissue to rather dense fibrous tissue. This consists in intertwining bundles of rather acellular tissue, in which the cytoplasm is denser and deeply stained. Occasionally there are present small islands of cartilage and/or bone. These, however, are adult in type and appear to represent inclusions rather than an integral part of the tumor. All sections are relatively avascular. The scattered capillaries are thin walled and engorged with blood. Occasionally there are foci of necrosis in the stroma.

The second conspicuous element in all the sections is the great number of giant cells of the epulis type. They vary somewhat in size, but all contain an abundant amount of deeply pink-staining cytoplasm and few to many centrally placed, round or oval, evenly stained nuclei. The sections taken from the periphery disclose a rim of dense fibrous tissue. Occasionally this contains a few spicules of adult bone and cartilage. None of the sections disclose evidence of malignant change.

Sections of the popliteal lymph nodes do not disclose any tumor involvement.

Pathologic Diagnosis.—The pathologic diagnosis was benign giant cell tumor.

Follow-Up.—When last seen, on April 23, 1945, two years and eight months after the first operation and ten months following amputation, the patient was in excellent health; he had gained 30 pounds (13.6 Kg.); the stump was well healed, and walking was satisfactory with the aid of a prosthesis. At this time roentgen ray examination of the long bones, pelvis, spine, skull and chest showed no evidence of metastatic lesions.

COMMENT

During the past twenty years 17 cases of giant cell tumor of bone have been encountered at the Jefferson Medical College Hospital, and in this group the case being reported is the only one in which pulsation

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EXPLANATION OF FIGURE 6

Photomicrographs of pulsating benign giant cell tumor. *A*, specimen obtained by curettement at first operation. Note the dilated vascular channels. *B*, specimen obtained following midthigh amputation twenty-two months later (×75).

was noted.[1] From the fact that only 7 cases, including ours, of pulsating benign giant cell tumor have been described in the literature since 1900 (table 1), one gains the impression that the lesion is exceedingly rare. Jaffe [2] stated that he encountered no aneurysmal or telangiectatic condition in his own material from giant cell tumors. Ewing,[3] on the other hand, referred to this lesion as "not much described in the literature, but not at all infrequent." Nové-Josserand and Tavernier,[4] in their book on tumors of the bone, stated that such forms are rather

TABLE 1.—*Summary of Cases of Pulsating Benign Giant Cell Tumor*

No.	Author	Year	Sex; Age; Trauma	Location	Treatment	Result
1.	Bloodgood, J. C.: Bull. Johns Hopkins Hosp. **14**: 134, 1903; Ann. Surg. **69**: 345, 1919	1903	M 26 +	Lower part of radius	Amputation of forearm below elbow	Well 25 yr. later
2.	Bloodgood, J. C.: Bull. Johns Hopkins Hosp. **14**: 134, 1903; Ann. Surg. **56**: 210, 1912	1903	F 45 —	Lower part of ulna	Resection of lower end of radius, ulna and first row of carpal bones	Well 15 yr. later
3.	Morton, J. J., and Duffy, W. C.: Arch. Surg. **7**: 469, 1923	1923	M 30 +	Upper part of tibia	Midthigh amputation	Well 14 yr. later
4.	Lewis, D.: (Cushing's case) J.A.M.A. **83**: 1224, 1924	1924	M 16 +	Lumbar portion of spine	Partial removal and subsequent roentgen therapy	Well 7 yr. later
5.	Mider, G. B., and Morton, J. J.: Ann. Surg. **109**: 126, 1939	1939	F 52 —	Ilium	Roentgen therapy followed by 6 partial excisions, ligation of internal iliac artery and application of radium	Death 1 yr. after first operation, from rapidly progressing intracranial lesion associated with signs of infection
6.	Scott [6] *	1942	F 24 —	Second metatarsal bone	Roentgen therapy (2 series)	Well 10 mo. later; swelling subsided and pulsation ceased
7.	Shallow and Wagner	1944	M 19 ?	Upper part of tibia	Curettage followed by roentgen therapy; subsequent midthigh amputation 22 mo. later	Well 10 mo. following amputation

* Pathologic diagnosis made by aspiration biopsy.

frequent in France and that they have observed several of them. They mentioned the cases of Rougthon, Borst, Luecke and Schleich but did not give references in the literature for them.

1. Shallow, T. A.; Raker, N., and Fry, K.: Primary Malignant Tumors of Bone with Special Reference to Osteogenic Sarcoma, J. Internat. Coll. Surgeons **6**:89, 1943.

2. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone, Arch. Path. **30**:993 (Nov.) 1940.

3. Ewing, J., in discussion on Peirce, C. B.: Giant-Cell Bone Tumor, Am. J. Roentgenol. **28**:167, 1932.

4. Nové-Josserand, G., and Tavernier, L.: Tumeurs malignes des os, Paris, Gaston Doin, 1927, p. 104.

The lesion represents a benign giant cell tumor which, apparently as the result of free communication with large blood vessels, grows to large size, pulsates and occasionally yields a bruit. Because the physical signs simulate those of true arterial aneurysm, the lesion has been regarded as a form of so-called bone aneurysm, a term that has been applied to pulsating, extremely vascular tumors of the bone. Ewing [5] referred to the lesion as "aneurysmal giant cell tumor" and classified it among the benign "bone aneurysms." Although the comparatively rapid growth and large size of the tumor create the suspicion of a malignant process, the benign character is demonstrated clinically by the long survival period and histologically by the absence of hyperchromatism, mitosis or the features of osteogenic sarcoma.

In the histologic picture alone, there is nothing which definitely differentiates the benign giant cell tumor which pulsates from the one in which this unusual clinical manifestation is absent. A tumor which appears extremely vascular histologically may lack pulsation clinically, while, on the other hand, a much less vascular one may exhibit this phenomenon to a pronounced degree. Indeed, all the histologic sections in our case at the time of amputation, when pulsation was most pronounced, were relatively avascular (fig. 6*B*). Thus pulsation depends primarily on the richness of arteriolar and arterial connections and not on the richness of the capillary network. It is natural to suppose that an extremely vascular tumor might be pulsatile, but an abundant capillary network poorly connected would not show pulsation.

Scott [6] emphasized the importance of the "tissue factors" in the pulsation sign. This term refers to a looseness and delicacy of the supportive stroma. Thus, the bone marrow normally pulsates, since the influx and reflux of blood in the thin-walled capillaries transmits the pulsation to the delicate and loose cellular tissue of the bone marrow. Scott [6] attributed the great tendency of secondary tumors of the thyroid and kidney to exhibit pulsation to this factor as well as the extreme vascularity.

Early observers were of the opinion that bone aneurysms were true aneurysms. While these tumors may present the physical signs of true arterial aneurysms, their causation and pathogenesis have little in common with that condition. They arise as neoplasms (primary sarcomas, metastatic tumors, hemangiomas or giant cell tumors),

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5. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

6. Scott, R. K.: Three Pulsating Tumors: Osseous Secondary from a Latent Carcinoma of the Kidney; Soft Tissue Secondary from a Latent Carcinoma of the Prostate; Benign Giant Cell Tumor of a Metatarsal Bone, Roy. Melbourne Hosp. Clin. Rep. **13**:76, 1942.

with dilated capillaries forming blood sinuses in free communication with their arterial supply in a poorly supportive stroma, such that the walls are easily distended by the pressure of each influx of blood. When the tumor erodes through the cortex, the pulsation may be detected clinically and the term "bone aneurysm" applied. However, the old claim of these lesions to separate classification has been disregarded, and at present the term has been almost universally abandoned.

The pulsation may vary in degree from such an extent that it raises the skin and is easily perceived by the eye to being so faint that it is palpable only by carefully regulated pressure with the pulp of the fingers. In cases with energetic pulsation a systolic bruit is usually present but a thrill seldom. The degree of pulsation will not establish the presence or absence of a malignant growth, but the existence of pulsation must be construed as an ominous sign.

The differential diagnosis of pulsating tumors of bone may in some instances be exceedingly difficult. Careful correlation of clinical roentgenologic and pathologic data is required (table 2).

Telangiectatic osteogenic sarcoma, referred to by Ewing [5] as "malignant bone aneurysm," usually occurs in young persons, grows rapidly, promptly destroys the shaft, leading to pathologic fracture, and as a rule terminates fatally, with metastasis, within a few months.

Pulsating metastatic carcinomas in bone are usually of thyroid or renal origin. Crile [7] (1936) collected from the literature 10 histologically verified cases of pulsating neoplasms of the sternum, of which five lesions were metastatic from hypernephroma and five from maligant adenoma of the thyroid. To these he added 5 proved cases from the Cleveland clinic, one of the lesions being metastatic from a hypernephroma and four from malignant thyroid adenoma. Alessandri [8] (1926) reported 4 cases of bone metastasis from hypernephroma, in 3 of which the neoplasms pulsated. In a review of the literature, he found that out of ninety-two such metastasic lesions twenty-seven were either of the pulsating type or of the highly vascularized type.

Hemangiomatous tumors of bone occasionally may pulsate. The malignant variety, hemangioendothelioma, is rare. Ewing [5] stated that he has seen 3 such cases, but Stout,[9] after reviewing the histologic description and illustration, cast doubt on their authenticity and expressed the opinion that they probably represented cases of metastases from hypernephroid carcinoma. Stout [9] has reported 2 cases of

7. Crile, G., Jr.: Pulsating Tumors of the Sternum, Ann. Surg. **103**:199, 1936.

8. Alessandri, R.: Sui tumori pulsanti delli osse ed in modo speciale sulle metastasi di ipernefromi nello scheletro, Policlinico (sez. chir.) **33**:273, 1926; abstracted, Cancer Rev. **2**:213, 1927.

9. Stout, A. P.: Hemangio-Endothelioma: A Tumor of Blood Vessels Featuring Vascular Endothelial Cells, Ann. Surg. **118**:445, 1943.

TABLE 2.—*Clinical, Roentgenologic and Pathologic Features in Differential Diagnosis of Pulsating Tumors of Bone*

TABLE 2.—*Clinical, Roentgenologic and Pathologic Features in Differential Diagnosis of Pulsating Tumors of Bone*

Features	Osteogenic Sarcoma (Telangiectatic)	Angioendothelioma	Metastatic Carcinoma	Giant Cell Tumor	Hemangioma
Clinical					
Typical age group	Children and young adults	Adults and elderly persons	Middle-aged and elderly persons	Young adults	Adults and middle-aged persons
Common locations..	Femur, tibia, humerus, pelvis and fibula	Long bones	Humerus, spine, femur, pelvis, ribs, skull and sternum	Femur, tibia, radius, humerus, maxilla and vertebrae	Vertebrae, skull, pelvis, scapula and long bones
Multiplicity.....	Single	Occasional	Frequent	Rare	Occasional
Rate of growth.....	Very rapid	May be rapid or slow	Ususally slow	Moderate	Slow
Roentgenologic.....	Erosion of shaft, often with radiating lines into subperiosteal area; periosteum elevated; medullary region usually shows some condensation	Destructive lesion, with widening of bones and fine irregular trabeculation	Cortical destruction, with no new bone formation or periosteal proliferation	Expanding, trabeculated, destructive lesion, with preservation of bony shell and multicystic appearance	Parallel vertical striations in vertebrae; sunburst trabeculation in flat bones; soap bubble appearance in long bones
Pathologic					
Origin.....	Primary	Primary or metastatic	Metastatic (usually from kidney or thyroid)	Primary	Primary
Character.....	Malignant	Malignant	Malignant	Usually benign	Benign
Histology.....	Pleomorphic osteoblasts in a mixed intercellular substance (hyalin, cartilaginous, myxomatous, osteoid or osseous), giant cells often present	Anastomosing vascular channels lined by heaped-up, atypical endothelial cells in a fibrous tissue stroma	Hypernephroma (large, clear cells in vascular scanty stroma) or malignant thyroid adenoma (resembling normal thyroid)	Giant cells in a stroma of spindle-shaped and round cells	Vascular elements (capillaries or cavernous spaces) in a fibrous tissue stroma

hemangioendothelioma of bone, but no mention is made of pulsation. He stated the belief that the diagnosis can be made with certainty only if two features are demonstrated: first, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane and, second, the formation of vascular tubes, with a delicate framework of reticulin fibers and a pronounced tendency for their lumens to anastomose.

Bucy and Capp,[10] in their review of hemangioma of bone, collected 3 cases from the literature in which pulsation was noted. Two tumors occurred in the skull (Schöne[11] and Zajaczkowski[12]) and one in the clavicle (Mauguière[13]). In these tumors there was an area of bony hardness at the periphery, raised above the level of surrounding bone, while the center was soft and pulsating.

If a true aneurysm develops in one of the branches of a main arterial trunk near the bone, it may cause a partial erosion and destruction of the bone. In such a case (Gaudier[14]), the roentgenologic appearance may resemble that of a tumor. Arteriography aids in distinguishing between true aneurysm and pulsating tumor of the bone. In addition, arteriography has been advocated by Inclan[15] for the early diagnosis of malignant growths of bone. The most characteristic arteriographic sign of malignant growths of bone is the filling in of the stroma of the new growth with numerous vessels, forming an erratic network and showing the extension of the invading tumor. This procedure may thus be of aid in the differentiation between benign and malignant bone tumors and may avoid the necessity of specimen and punch biopsy, which has been claimed to spread tumor cells into the venous circulation by rupturing these structures. Arteriography is not without danger, however, and the possible complications have recently been reviewed by one of us.[16]

Diagnosis of the benign nature of a pulsating giant cell tumor is not only difficult but also dangerous from the standpoint of treatment

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10. Bucy, P. C., and Capp, C. S.: Primary Hemangioma of Bone, Am. J. Roentgenol. **23**:1, 1930.

11. Schöne, G.: Ueber einen Fall von myelogenem Hämangiom des Os occipitale, Beitr. z. path. Anat. u. z. allg. Path. (supp.) **7**:685, 1905.

12. Zajaczkowski, A.: Ein Fall von Angioma cavernosum des Stirnbeines, Przeg. chir. **4**:606, 1900; abstracted, Centralbl. f. Chir. **28**:507, 1901.

13. Mauguière, L.: Angiosarcome de la clavicule, J. de radiol. et d'électrol. **4**:269, 1920.

14. Gaudier, cited by Nové-Josserand and Tavernier,[4] p. 272.

15. Inclan, A.: The Possibilities of the Roentgenographic Study of the Arterial Circulation in the Early Diagnosis of Bone Malignancy, J. Bone & Joint Surg. **24**:259, 1942.

16. Wagner, F. B., Jr.: Complications Following Arteriography of Peripheral Vessels, J. A. M. A. **125**:958 (Aug. 5) 1944.

because of the constant threat of malignant growth. In spite of careful attempts to correlate the clinical, roentgenologic and pathologic data, there are still possibilities of error in the diagnosis of giant cell tumor, as pointed out by Codman.[17] In the first place, the roentgenograms may be characteristic but the histologic picture in favor of some other diagnosis. On the other hand, from both the roentgenograms and the slides the tumor may be interpreted as giant cell tumor, and yet the case may run a rapidly fatal course, indicating that an error was made. Finally, the roentgenograms, sections and clinical course may apparently assure the diagnosis, and yet a sarcoma may eventually appear at the site of the lesion.

Whenever possible, the treatment for pulsating benign giant cell tumor of bone should be wide surgical resection of the involved area. Scott [6] has reported a case in which the swelling and pulsation subsided after roentgen therapy and in which the patient was well ten months later. A much longer period of follow-up is needed, however, to demonstrate the complete efficacy of this form of therapy. Ewing [3] stated that "they do not do particularly well with irradiation and generally terminate in amputation." Although the reported cases are too few to justify definite conclusions, it appears safest at present to reserve roentgen therapy as an adjunct to surgical treatment, particularly for areas of the body in which resection is infeasible and curettage must be employed.

The prognosis as to life itself is good, but in 3 out of the 7 cases a limb was eventually sacrificed. The prognosis locally can be improved by earlier diagnosis and prompt surgical treatment, thus entailing less resection of bone, with resultant decrease in deformity and loss of function.

SUMMARY AND CONCLUSIONS

1. A case of pulsating benign giant cell tumor of bone is presented in detail, and 6 additional cases from the literature since 1900 are reviewed. It is improbable that the lesion is so rare as these few reports would indicate.

2. The histologic picture is indistinguishable from the ordinary variety of giant cell tumor. The pulsation probably depends on free communication of the capillary network of the tumor with its arteriolar and arterial supply, looseness of the supportive stroma and erosion of the bony cortex.

3. This tumor must be differentiated from other pulsating tumors of bone, namely telangiectatic osteogenic sarcoma, metastatic carcinoma

17. Codman, E. A.: Treatment of Giant Cell Tumors About Knee, Surg., Gynec. & Obst. **64**:485, 1937.

from the thyroid or kidney and benign and malignant hemangiomatous tumors. Careful correlation of clinical, roentgenologic and pathologic data is required.

4. Treatment should consist in wide surgical resection of involved bone whenever possible. If this procedure is impractical, curettage supplemented by irradiation therapy may be employed.

5. The prognosis as to life is good, although amputation may eventually be required. Earlier diagnosis and prompt surgical treatment will lessen the degree of postoperative deformity and loss of function.

INJECTION INTO PERICARDIAL SAC AND LIGATION OF CORONARY ARTERY OF THE RAT

ROBERT F. HEIMBURGER, M.D.
DURHAM, N. C.

ACTIVE interest in surgical methods by which deficient circulation in the coronary artery might be supported through collateral vessels was initated by Beck. This author, as a result of his experiences with the injection of diluted solution of sodium hypochlorite into the pericardial cavity of dogs [1] and of the observations of Hudson, Moritz and Wearn [2] and of Moritz, Hudson and Orgain [3] related to autopsy study of extracardiac circulation in human hearts, began the series of experiments leading to the operations on patients summarized by Beck [1] and by Feil.[4] In current surgical clinical efforts toward the development of extracardiac circulation, openings in the pericardium have been employed through which pectoral muscle or mediastinal fat, (Beck [5]) or omentum (O'Shaughnessy [6]) was brought to the heart.

Many investigators have employed irritants to obliterate the pericardial sac by adhesions or to cause grafts to adhere. Beck [5] employed abrasion and powdered asbestos, and O'Shaughnessy [6] used aleuronat with these grafts in patients. Adhesions of the pericardial sacs of patients have been sought by open injections of aleuronat, lionite (impure native tellurium) and sodium morrhuate by Heinbecker and Barton [7] and purified talc by Thompson and Raisbeck.[8] Rákov [9]

From the Department of Surgery, Duke University School of Medicine.

1. Beck, C. S.: The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, Arch. Surg. **18**:1659 (April) 1929.

2. Hudson, C. L.; Moritz, A. R., and Wearn, J. T.: The Extracardiac Anastomoses of the Coronary Arteries, J. Exper. Med. **56**:919 (Dec.) 1932.

3. Moritz, A. R.; Hudson, C. L., and Orgain, E. S.: Augmentation of Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions, J. Exper. Med. **56**:927 (Dec.) 1932.

4. Feil, H.: Clinical Appraisal of the Beck Operation, Ann. Surg. **118**:807 (Nov.) 1943.

5. Beck, C. S.: Principles Underlying the Operative Approach to the Treatment of Myocardial Ischemia, Ann. Surg. **118**:788 (Nov.) 1943.

6. O'Shaughnessy, L.: Surgical Treatment of Cardiac Ischemia, Lancet **1**:185 (Jan. 23) 1937.

7. Heinbecker, P., and Barton, W. A.: An Effective Method for the Development of Collateral Circulation to the Myocardium, Ann. Surg. **114**:186 (Aug.) 1941.

(Footnotes continued on next page)

injected sodium morrhuate into the pericardial sacs of 2 patients by needle puncture without open operation.

In early experiments, both the formation and the vascularity of adhesions produced by several substances have been studied. Schildt, Stanton and Beck [10] employed croton oil, oil of santal, solution of formaldehyde, acriflavine, sodium ricinoleate, iodochlorol, tragacanth, purified talc, purified siliceous earth, sand, agar, cotton, aleuronat, lionite and asbestos experimentally. Powdered asbestos was finally chosen for use clinically. Heinbecker and Barton [7] used aleuronat, lionite and sodium morrhuate but discarded these substances for a semisolid mixture of gelatin, aleuronat, starch, glycerin, lionite and water. O'Shaughnessy [11] has used aleuronat and a mixture of aleuronat, starch and glycerin. Scola and Stoesser [12] advocated the use of lycopodium. Additional experimental studies of other graft materials, such as the lung, have been made by Lezius,[13] and studies of other injection materials have been reviewed by the aforementioned authors.

The importance of the use of irritants alone or with cardiac grafts has encouraged this study. Experiments on the rat have been devised to further investigate the effectiveness of several of the aforementioned irritants and of new irritants in the production of adhesions. Experiments were also performed to determine by ligation of the coronary artery the possible effectiveness of the adhesions.

METHOD

Three hundred and eight male and female white rats weighing 200 to 300 Gm. were employed. The injection material was introduced through a 24 gage needle directly into the pericardial sac, which was exposed by a small thoracotomy wound, with the animal under positive pressure ether anesthetic. Ligation of the coronary artery was performed through a slightly larger thoracotomy wound. The incision in the pericardium for ligation of the artery was made over the medial border of the left auricle. The artery or the artery and the vein or, in some experiments, only the vein was doubly ligated with 000000 silk sutures between

8. Thompson, S. A., and Raisbeck, M. J.: Cardio-Pericardiopexy: The Surgical Treatment of Coronary Arterial Disease by the Establishment of Adhesive Pericarditis, Ann. Int. Med. **16**:495 (March) 1942.

9. Rakov, H. L.: Therapeutic Pericarditis by Intrapericardial Injection in Chronic Coronary Insufficiency, Am. Heart J. **23**:803 (June) 1942.

10. Schildt, P.; Stanton, E., and Beck, C. S.: Communications Between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart, Ann. Surg. **118**:34 (July) 1943.

11. O'Shaughnessy, L.; Slome, D., and Watson, F.: Surgical Revascularisation of the Heart: Experimental Basis, Lancet **1**:617 (March 18) 1939.

12. Scola, J. V., and Stoesser, F. G.: The Use of Lycopodium as an Agent to Create a Collateral Circulation to the Myocardium from the Pericardium, Surg., Gynec. & Obst. **79**:497 (Nov.) 1944.

13. Lezius, A.: Die künstliche Blutversorgung des Herzmuskels, Arch. f. klin. Chir. **189**:342, 1937.

the aorta and the division of the coronary artery into the descending and circumflex branches. Observations were made at intervals during surgical exploration or during autopsy.

INJECTION INTO THE PERICARDIAL SAC

Isotonic solution of sodium chloride, 0.2 cc., was injected into the pericardial sacs of each of 20 rats to control the effect of exposure and injection. The hearts of the rats were examined in pairs by surgical exposure or by autopsy at daily intervals up to ten days. The pericardia and the hearts appeared normal. Adhesions or exudates were not observed.

Twenty-five irritating materials and certain combinations were then injected into additional animals to determine their adhesion-pro-

TABLE 1.—*Effects of Injection of Several Materials for Production of Pericardial Adhesions Between Heart and Pericardium*

Substance	Rats, No.	Adhesions		Without Adhesions, No.	Foreign Body Reaction		Pleural Effusion, Degree
		No.	Degree		No.	Degree	
Acids	24	14	+	10	0	..	++++
Oils	11	2	+	9	7	+++	+
Cod liver oil and trichloroacetic acid, 2.5%	2	2	++	0	2	++++	++
Proteins	22	0	..	22	16	++	0
Lycopodium combinations	12	9	+++	3	11	+++	+
Alcohol, 7%	2	0	..	2	0	..	0
Powder of purified siliceous earth in isotonic solution of sodium chloride	2	0	..	2	2	+++	0
Urea, 20%	2	0	..	2	0	..	0
Sodium salicylate, 20% aqueous	2	0	..	2	0	..	0

ducing properties. The materials employed are loosely grouped for presentation into acids, oils, protein, lycopodium, miscellaneous materials and detergents.

Acids.—The effects of injecting the several acids into the pericardial sacs of 26 rats are presented in table 1. Acetic acid was employed as a 1.5 per cent and as a 3 per cent solution in sterile water. The 1.5 per cent solution injected into 2 rats produced no adhesions during eighteen days. One of 2 rats into which the 3 per cent solution was injected died after two days of fibrinous adhesions. Hydrochloric acid, tenth-normal, produced no adhesions after fourteen days in 2 rats. Ascorbic acid, 0.5 per cent, produced no adhesions after twenty-five and ninety days in 2 rats. Trichloroacetic acid, 1 per cent, produced no adhesions after twelve days in 2 rats. Trichloroacetic acid, 2 per cent produced fine loose adhesions after sixteen days in 2 rats. Trichloroacetic acid, 2.5 per cent, was injected into 12 rats. Respiratory difficulty developed in 7. When examined at autopsy or killed within

two days of the injections, they had extensive pleural effusion. The pericardial spaces contained fibrinous adhesions. There was dilatation and injection of vessels in the hearts and pericardia. There was also some free fluid. Two rats killed at five days and 1 at ten had fine friable adhesions. Two rats killed at eleven days had no adhesions. Three per cent trichloroacetic acid produced prompt death in 2 rats. Acids in general were poorly effective in the production of adhesions and tended to produce excessive effusion into the adjacent pleural cavity, with respiratory difficulty.

Oils.—The effects of injecting the several oils used into the pericardial sacs of 11 rats are presented in table 1. Iodochlorol (Searle) injected into 2 rats produced foreign body reaction. This consisted in the development of granulation tissue over the heart or the surface of the pericardia. The oil was walled off or pocketed. There were no adhesions after twenty-five days. Roentgen ray examination demonstrated that the oil spread through the pericardial space. Peanut (arachis) oil produced a similar foreign body reaction in 2 rats. One of them had a few scattered adhesions. Cottonseed oil injected into 2 rats killed at ten and twenty-five days seemed to have disappeared without producing adhesions or significant foreign body reaction. Cod liver oil injected into 3 rats killed after ten days produced foreign body reaction without adhesions. Cod liver oil and a 2.5 per cent solution of trichloroacetic acid were injected into 2 rats. They produced firm bands of adhesions enclosing pockets of foreign body granulation tissue and cod liver oil after twelve days. Plantago oil (Searle) produced death in 1 animal after two days of pleural effusion. In another animal killed after eleven days, it produced an extensive exudative reaction in the left side of the chest and, in addition, many constricting bandlike adhesions. Oils in general seem to produce foreign body reactions without effectively producing adhesions.

Proteins.—Proteins were injected into the pericardial spaces of 22 rats to determine their effectiveness in the production of adhesions (table 1). Clotted human fibrinogen, fresh human plasma and fresh egg albumin were each injected into 2 rats. Adhesions did not develop during ten days of observation. The pericardial sacs appeared normal. Chromicized surgical gut was powdered, suspended in isotonic solution of sodium chloride and injected into 16 rats. It produced a granulomatous foreign body reaction but did not produce adhesions after ten to fourteen days. The proteins used did not produce adhesions.

Lycopodium.—The effect of injection of lycopodium into the pericardial sac was tested by insufflation of the dry powder through a needle and by introduction of it as a suspension in the oils previously described in 12 rats (table 1). Insufflation was employed in 2 rats. In

1 adhesions developed over a portion of the heart by twelve days. The other rat, killed after the same time, had none. In 2 rats into which lycopodium powder in cottonseed oil was injected, adhesions and foreign body reaction developed in ten days (fig. 1). The suspension in peanut (arachis) oil developed foreign body reaction without adhesions in 2 rats after ten days. The suspension in cod liver oil in 2 rats produced extensive foreign body reaction with a few adhesions ten days after injection. Lycopodium suspended in iodochlorol (Searle) produced a few adhesions and considerable foreign body reaction after ten day in 2 rats. Lycopodium powder and sodium morrhuate, 5 per cent (Searle), in 2 rats obliterated the pericardial spaces. The hearts and the pericardia were involved in foreign body reaction after ten days. The better adhesions of this group were formed by

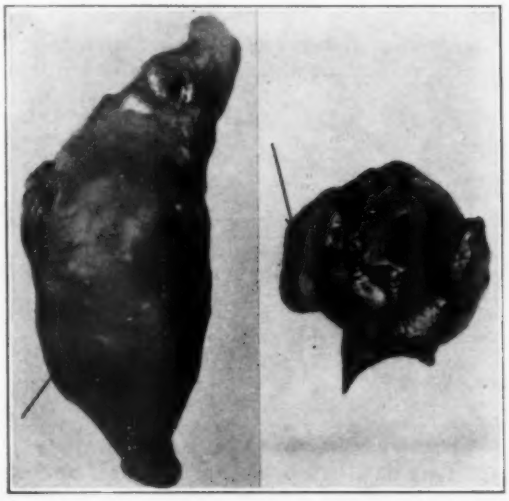

Fig. 1.—Profile and cross section views of the heart of a rat ten days after injection of lycopodium suspended in 0.2 cc. of cottonseed oil into the pericardial sac. The granulomatous foreign body reaction typical of that observed after other oils is indicated by the arrows.

lycopodium powder suspended in cottonseed oil, iodochlorol or 5 per cent sodium morrhuate (Searle). The foreign body reaction around the lycopodium particles was occasionally extensive and caused cardiac constriction.

Miscellaneous Substances.—Alcohol, purified siliceous earth and isotonic solution of sodium chloride, urea and sodium salicylate were each injected into the pericardial sacs of 2 rats (table 1). Ethyl alcohol, 7 per cent, did not produce a detectable reaction within fourteen days of the injection. Purified siliceous earth suspended in isotonic solution of sodium chloride produced discrete areas of foreign

body reaction and no adhesions during nine days. An aqueous urea solution (20 per cent) did not produce adhesions during eighteen and forty days. An aqueous sodium salicylate solution (20 per cent) produced no detectable reaction during nineteen days. Croton oil, full strength; quinine hydrochloride and ethyl carbamate (Lilly), full, half and quarter strengths; sodium salicylate, half strength, and Aerosol, OT, quarter strength, each injected into the pericardial sacs of 2 rats produced cardiac contracture and instantaneous death.

Detergents.—Five salts of fatty acids and two combinations with other material were injected into the pericardial sacs of 128 rats (table 2). A 5 per cent aqueous solution of sodium stearate produced no adhesions in 2 rats during a ten day period. Aerosol, a 5 per cent aqueous solution, was injected into 12 rats. Four died within three

TABLE 2.—*Effects of Injection of Several Detergents for the Production of Adhesions Between Heart and Pericardium*

Substance	Rats, No.	Adhesions		Without Adhesions, No.	Foreign Body Reaction		Pleural Effusion, Degree
		No.	Degree		No.	Degree	
Sodium stearate, 5%.....	2	0	..	2	0	0	0
Aerosol O T, 5%.....	12	5	+++	7	0	0	++++
Castile soap.....	17	9	+++	8	0	0	0
Castile soap, 20%, and trichloroacetic acid, 2.5%.....	2	1	++++	1	0	0	+
Sylnasol, 20%.....	5	5	++++	0	0	0	+++
Sylnasol, 5% (Searle).....	2	1	+++	1	0	0	++
Sodium morrhuate, 20%.....	26	20	++ to ++++	6	0	0	++
Sodium morrhuate, 5%.....	86	53	++	33	0	0	++
Sodium morrhuate, 5%, and iodochlorol.....	2	1	++++	1	0	0	++

hours and 1 after two days from pleural effusion and respiratory difficulty. Seven were killed at ten days. Four had firm adhesions and 1 partial adhesions. Two had no adhesions. Castile soap, a 5 per cent aqueous solution, was injected into the pericardial sacs of 17 rats killed at ten days. Three had complete firm adhesions and 6 partial adhesions. Eight had no adhesions. Pleural effusion was not observed. A 20 per cent solution of the salts of certain fatty acids of oil from a seed of the psyllium group in 5 rats produced complete but loose adhesions of the hearts and the pericardia after ten days and in 3 rats complete firm adherence without constriction after nine months. Sylnasol in 2 rats produced similar but less extensive changes. Twenty per cent sodium morrhuate (Searle) was injected into 26 rats. In 7 complete adherence developed at the time of autopsy ten or more days after injection. In 13 fibrinous adhesions developed one to five days after injection. Six rats examined at autopsy ten minutes, twenty-four hours, four days

and nine months after injection had no adhesions. In 86 rats, 2 cc. of 5 per cent sodium morrhuate containing 2 per cent benzoic acid (Searle) was injected. In 21 complete adherence between the hearts and the pericardia developed between ten and two hundred and twenty-four days. The adhesions were seen at autopsy or subsequent operation (fig. 2). Fifteen examined at autopsy or exposed at operation between four and ten days after injection had firm adhesions. Eighteen rats killed twenty-four hours to nine days after injection had exudate with fibrinous adhesions over the entire surface of the heart. Seven examined at autopsy twenty-seven, thirty-six, fifty-three, fifty-three, fifty-eight, seventy-six and ninety-one days after injection had only partial adherence between the hearts and the pericardia. In 33 of the 86 rats given injections of 5 per cent sodium morrhuate, no adhesions developed.

Fig. 2.—Profile and cross section views of the heart and pericardium two hundred and twenty-four days after injection of 0.2 cc. of 5 per cent sodium morrhuate. The pericardium is completely adherent to the heart. Adhesions are fine and firm. Foreign body reaction is not present.

Twenty-three of them were examined less than nine days after the injection and 10 examined later than ten days. In all the rats into which 5 per cent sodium morrhuate had been injected some respiratory difficulty developed after operation but less than in those in which 20 per cent sodium morrhuate had been employed. In 1 of 2 rats into which a mixture of equal quantities of sodium morrhuate, 5 per cent, and iodochlorol was injected firm adhesions developed over the entire heart after ten days. The other, examined at the same time, had no adhesions. An aqueous solution of equal parts of castile soap, 20 per cent, and trichloroacetic acid, 2.5 per cent, was injected into 2 rats. In 1, complete firm adhesions developed within ten days between the heart, the pericardium and the thoracic wall. In the other, adhesions did not

develop during ten days. Many detergents effectively produced adhesions. Castile soap was interesting, since it produced adhesions without producing effusion into the adjacent pleural cavity.

LIGATION OF THE CORONARY ARTERIES IN RATS USED AS CONTROLS

Ligation of the left or the right coronary artery or the coronary vein was attempted in 30 normal rats. Twelve more, into which isotonic solution of sodium chloride had been previously injected and without pericardial adhesions at the time of ligation, were also used. Ligation of the left coronary artery, often including the vein, was attempted and examined during autopsy in 34 of these 42 animals. Complete coronary occlusion was effected in 13 rats and probable in 1. The rats listed here and in the following paragraphs as having probable ligation of the

TABLE 3.—*Definite or Probable High Ligation of the Left Coronary Artery*

	Animals with Coronary Occlusion	Death During First 24 Hours *	Death after 24 Hours	Killed with Damage to Heart	Killed Without Significant Damage to Heart
Ligation of coronary artery of normal rats	14	3	2	7	1
Ligation within 10 days of injection (heart adherent)	5	3	1	0	1
Ligation within 10 days of injection (no adhesions)	6	2	3	0	0
Ligation 14 to 50 days after injection (heart adherent)	16	3	0	8	3
Ligation 14 to 50 days after injection (no adhesions)	7	1	1	3	2

* Four rats dying during operation from anesthetic or from hemorrhage are excluded from this table.

coronary artery are those that had sufficient density of adhesions at the time of autopsy to obscure accurate visualization of the artery. The ligature was correctly placed. A summary of the effect of complete or probable occlusion is given in table 3. Complete occlusion was associated with death within ten minutes in 3 of the 13 normal rats. Two were killed at twenty-four hours and had extensive necrosis of the left ventricle. One died five days after ligation, with a thin and dark left ventricle. One died fourteen days after ligation from pulmonary congestion and pleural effusion. The entire left ventricle was scarred. Five were killed at fourteen, twenty-one, twenty-one, twenty-three and forty-one days and had large, dilated, thin, scarred left ventricles (fig. 3) or extensive fibrosis, thinning and scarring (fig. 4). One with a probable occlusion of the left ventricle was killed after fifteen days, and adhesions had developed. The cardiac wall showed little scarring. One animal with complete occlusion died of hemorrhage at operation. Autopsy

revealed faulty or low ligature without complete occlusion in 20 of the 34 rats. These animals were killed after a period of twenty-four hours to seven months. Localized adhesions had developed near the ligature in 9. The hearts of 4 rats showed small areas of infarctions.

Ligation of the right coronary artery was attempted in 3 of the 40 rats. One died at operation, and 1 had a faulty position of the suture. The third, killed twenty days after ligation, showed definite occlusion of the right coronary artery, with pronounced fibrosis and scarring of the entire right ventricular wall.

The left coronary vein alone was ligated in 5 of the 40 rats. Examination after ten days revealed no significant pathologic change.

Fig. 3.—The thin, scarred, dilated left ventricle of a rat killed twenty-one days after ligation of the left coronary artery.

INJECTION WITH SODIUM MORRHUATE AND LIGATION OF THE CORONARY ARTERY

Ligation of the left coronary artery was attempted and examined during autopsy in 46 rats previously treated by injection of sodium morrhuate. Ligation was performed within ten days of the injection (average five days) in 18 rats and between fourteen and fifty days (average forty-five) in 28. In 7 of the 18 rats that had ligation within ten days of the injection, adhesions had developed. Complete coronary occlusion was effected in 5 (table 3). It was associated with death

within ten minutes in 3. Complete coronary occlusion was associated with death in 1 in twenty-four hours and in another, that had pleural effusion, in fourteen days. The hearts in neither animal showed infarction. The coronary occlusion was not complete in 1 killed twenty-eight days later. One rat died of hemorrhage during operation.

Eleven of the 18 rats had no adhesions by the average time of five days that preceded ligation of the coronary artery. Complete coronary occlusion was effected in 5 and probable in 1 (table 3). Complete coronary occlusion was associated with death within ten minutes in 2.

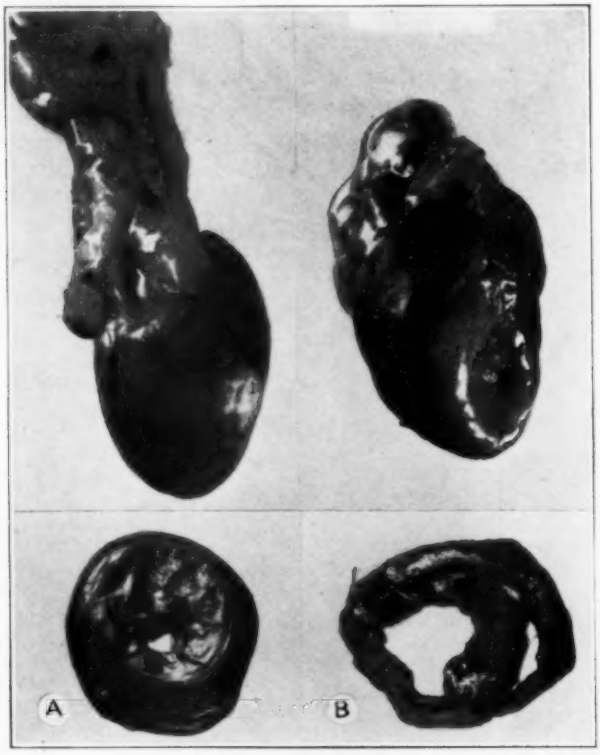

Fig. 4.—Profile and cross section views comparing the heart of a normal rat, *A*, with a fibrosed, thinned, scarred heart twenty-three days after ligation of the left coronary artery, *B*.

Complete occlusion produced death from infarction of the cardiac wall and pleural effusion in 1 rat at three days and in 1 at eleven. Another died at nine days of pleural effusion but without infarction. One, killed thirty days after operation, had probable occlusion, and firm adhesions had developed without infarction. Of the 5 remaining rats, 2 had the ligatures below the bifurcation of the artery. This was associated with death from pleural effusion in 1 within twenty-four hours, and autopsy

at thirty days in 1 revealed that adhesions had developed since ligation but that there was no cardiac infarction.

The artery was missed in the remaining 3. One died at six days, of undetermined cause, and 2 were killed at thirty-two days and had firm adhesions.

In 19 of the 28 rats that had ligation fourteen to fifty days after injection, adhesions had developed by the average time of forty-five days, at which time ligation of the coronary artery was attempted. Complete coronary occlusion was demonstrated in 13 rats and probable in 3

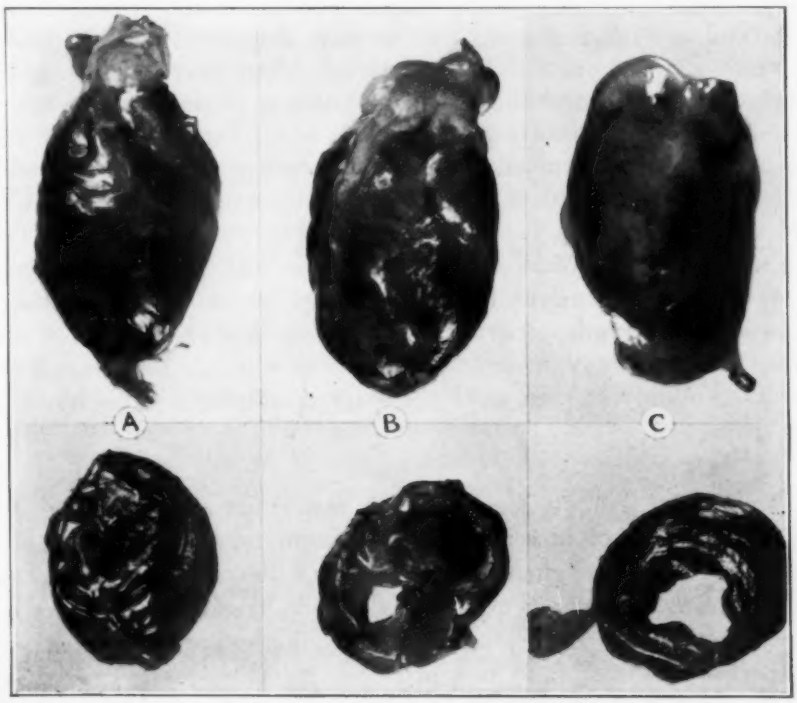

Fig. 5.—Profile and cross section views of three hearts with adhesions produced by injection of sodium morrhuate into the pericardial sacs forty-nine, twenty-seven and fifty-four days before ligation of the left coronary artery. The first rat (*A*) was killed for examination thirteen days after probable complete occlusion, the second rat (*B*) twenty-eight days after definite complete occlusion and the third rat (*C*) nineteen days after definite complete occlusion. Moderate thinning, fibrosis and dilatation have occurred in *B* and in *C*.

(table 3). Two rats died at operation of hemorrhage. Occlusion was associated with death within ninety minutes in 3 rats. Eight were killed at thirteen, fourteen, sixteen, nineteen, thirty-four, thirty-six, thirty-six and fifty-four days respectively and had thinning and scarring of the wall of the ventricle (fig. 5 *B* and *C*). Three others had probable occlusion and when killed at thirteen, fourteen and thirty-six days had dense

adhesions without myocardial damage (fig. 5 *A*). Ligation was low in 1 killed at fifty-five days. Adhesions were present without cardiac scar. The artery was missed in the remaining 2, and at autopsy at fourteen days adhesions were present without damage to the cardiac wall.

In 9 of the 28 rats given injections an average time of forty-five days no adhesions had developed at the time of attempted ligation of the coronary artery, and complete occlusion of the coronary artery was effected in 5 and probable in 2 (table 3). Complete occlusion was associated with death at operation in 1. It was associated with death at eight days in another from an undetermined cause. Adhesions had not developed. Three animals with complete occlusion were killed at thirteen, twenty-eight and one hundred and fifty-four days respectively and had large scars in the wall of the left ventricle. There were no adhesions. Probable coronary occlusion in 2 rats killed at thirteen and at thirty-five days was associated with no damage to the cardiac wall and with the development of firm adhesions. The coronary artery was missed in the remaining 2, killed at eleven days, without damage to the heart and with adhesions in 1.

Injection of 2 cc. of 5 per cent sodium morrhuate was also performed in 4 rats that had survived occlusion of the coronary artery between three and nine days respectively. One died the day after injection, with necrosis of the left ventricle and fibrinous adhesions. Two were killed at fifty-two and fifty-four days and showed adhesions and scarring of the ventricle.

SUMMARY

The use of irritating agents in the pericardial sac or between the heart and grafts of muscle, fat or omentum to secure adhesions or extracardiac collateral circulation in patients with coronary heart disease has stimulated this study of irritants and of ligation of the coronary artery in the rat. Isotonic solution of sodium chloride injected into the pericardial sacs of 20 rats produced no adhesions. Twenty-five irritating materials and certain combinations were introduced by needle puncture into the exposed pericardial sacs of 246 rats. Acetic acid, hydrochloric acid, ascorbic acid and trichloroacetic acid were used in 26 rats and found poorly effective in the production of adhesions. They produced effusion into the adjacent pleural cavities. Iodochlorol, peanut (arachis) oil, cottonseed oil, cod liver oil and plantago oil were used in 11 rats. They produced extensive granulomatous foreign body reaction and few adhesions. Clotted human fibrinogen, human plasma, egg albumin and chromicized surgical gut were used in 22 rats. They did not produce adhesions. Lycopodium suspended in several oils was used and produced extensive foreign body reactions in 10 rats. Alcohol, purified siliceous earth and isotonic solution of sodium chloride, urea

and Aerosol were each used in 2 rats, often in several strengths, with the varying results described and without good adhesions. Sodium stearate produced no adhesions in 2 rats. Aerosol produced adhesions in 5 of 12 rats. Pleural effusion and respiratory difficulty occurred. Castile soap produced adhesions in 9 of 17 rats and did not produce foreign body reaction or pleural effusion. Sylnasol produced firm adhesions in 10 rats. Twenty per cent sodium morrhuate was used in 26 rats and produced fibrinous or fibrous adhesions in 20. Two rats at ten days and seven months had no adhesions. Four examined before ten days also had no adhesions. Five per cent sodium morrhuate was employed in 86 rats. It produced adhesions in all but 23 examined at less than nine days and 10 examined at more than ten days. Effusion into the adjacent pleural cavity and respiratory difficulty were often encountered.

Ligation of coronary vessels was employed in 42 normal rats. Ligation of the left coronary vein alone in 5 produced no significant pathologic change. Ligation of the right coronary artery was performed in 3, with fibrosis and scarring of the right ventricular wall in 1. Ligation of the left coronary artery was attempted in 34 and successful in 14. Scarring, fibrosis and dilatation of the left ventricle developed in 7.

Ligation of the left coronary artery was attempted in 46 rats after injections of the pericardial sacs with sodium morrhuate. It was successful in 34. Twenty-one had adhesions at the time of the ligation, and 13 did not have adhesions. The effect of the ligation in each group is summarized in table 3. Injections of sodium morrhuate in 4 rats that had survived occlusion of the left coronary artery three to nine days did not prevent death in 2 or damage to the ventricle in 2.

CONCLUSIONS

Many substances produce adhesions when injected into the pericardial sac of the rat. They also produce reactions or complications. Acids produce effusion. Oils and lycopodium in oil produce granulation tissue and foreign body reaction. Detergents produce firm adhesions. Sodium morrhuate produces adhesions and moderate effusion. Castile soap produced adhesions without producing foreign body reaction or effusion into the adjacent pleural cavity.

Ligation of the coronary artery more than ten days after the injection of sodium morrhuate and the development of adhesions of the pericardial sac is associated with as high an immediate mortality and as frequent an occurrence of survival with damage to the heart as observed in the rats used as controls. The degree of damage is slightly less. Ligation within ten days before or after injection is poorly tolerated.

Keith S. Grimson offered encouragement and advice during the experiments and the preparation of this report.

PILONIDAL SINUS

A Review of 130 Consecutive Cases in Which Patients Were Treated by Closure; A New Closed Operative Method and Management

COMMANDER CHARLES E. POPE (MC) U.S.N.R.
AND
CAPTAIN HENRY W. HUDSON (MC) U.S.N.R.

THIS article is a summary of the methods of treatment and the results obtained in the treatment of pilonidal sinus in a ward devoted mainly to proctologic cases at the United States Naval Hospital Chelsea, Mass.

In a relatively short period a large number of patients were seen and operated on. In a relatively short period these patients were dismissed free of symptoms and, providing recurrence is not experienced at a later date, which is unlikely in the vast majority, cured. We believe that we are now justified in stating that a new closed operative method can be described, applicable in virtually all cases of pilonidal sinus. We realize that this is a rather sweeping claim to make, but only the extremely rare case will not permit this, such as that in which bone involvement or spinal canal or dural involvement coexist. For in this series not only was the usual simple sacrococcygeal type seen, but many cases also in which involvement was so extensive that any type of previously described closed method could not be used successfully. All cases were consecutive, and all sinuses were resected and closed. The diagnosis was confirmed pathologically in all instances. This paper reviews and evaluates the new method, comparing the usual type of simple closure with that of the new method. The actual operative steps and its description are left to an accompanying article.

The average age of the patients was 23.4 years. Though some patients were obese and some hairy, suggesting an endocrine disturbance, it could not be said to be so in the majority of instances. We suggest that the large number of patients in this age group is caused by sudden stress and strain in a class of persons not properly adapted or accustomed to a rigorous physical program. Inflammation of a pilonidal

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tract, therefore, is more apt to occur from trauma in military life than in civilian life.

Many articles have been written on the surgical treatment of pilonidal cyst, with considerable confusion resulting because of methods described as applicable to certain types and not applicable to others and in other instances because of methods not in keeping with advanced therapy.

We are in agreement with Magrath,[1] who stated that, through lack of clarity and misunderstanding of the type of pilonidal cyst operated on, many methods described in the past have led to discouraging results. We also agree with him that the name pilonidal cyst is a misnomer and that a pilonidal cyst is in reality a "raphe (epithelial) inclusion."

This study is a surgical review of 130 cases seen consecutively during a period shortly over six months. All the one hundred and thirty cysts were sacrococcygeal in location, were at least recently inflammatory, were symptomatic and in all instances were operated on by a closed procedure. That this was possible in all cases was due to careful preoperative and postoperative care, the use of sulfonamide therapy and penicillin and last, but not least, the application of the new operative procedure. Since the results have lowered the stay of hospitalization even over that of our predecessor, Dr. H. E. Kennard,[2] who reported excellent results obtained in a series of 50 cases of operation by simple closure, we believe that it is a method worthy of careful consideration. There is no method of treatment, however, but can be improved, and even during the short course of this series changes and improvements were made. Dr. Kennard, in his preceding series, established certain steps in the regimen of preoperative and postoperative treatment, as well as in his surgical technic, which in many details deserved duplication.

PREOPERATIVE CARE OF THE PATIENT

Although eleven of the one hundred and thirty cysts were quiescent at the time of operation, all patients not demonstrating a definite sinus, with its dimple and signs of resolving inflammation or active inflammation, coupled with a history of definite troublesome symptoms were refused operation. This meant that many patients required incision and drainage of the abscess, hot wet boric packs and sitz baths preoperatively. One hundred and nineteen cysts were termed inflammatory either by reason of the pathologic report or by the definite demonstration of purulent discharge. One quiescent lesion was a cystic type, only chronically inflamed. The patients with cysts incised and drained were

1. Magrath, J. L.: Pilonidal Sinus or Cyst: A Misnomer, Am. J. Surg. **64**: 101-103 (April) 1944.

2. Kennard, H. S.: A Method to Shorten Hospitalization of Patients with Pilonidal Cysts, Mil. Surgeon **97**:132-135 (Aug.) 1945.

hastened to operation much sooner than was desired, owing to an exceptionally crowded hospital and the need for a rapid turnover. Such patients averaged only two to ten days of preoperative care as compared with the twenty-seven days averaged by Kennard. Many patients were operated on with cysts in fairly active stages of inflammation. This led to an occasional soiled operative field, and, though in many cases no untoward result occurred, the results would have been better if more time and a totally quiescent lesion had been assured preoperatively.

The immediate preoperative steps were directed toward the obtaining of a clean field for operation and in cleansing enemas to prevent bowel movement postoperatively. The day before operation the patient was showered and bathed, the hair shampooed and the nails scrubbed. The pubic, perineal, sacral and anal hair was shaved over a wide expanse. Four quart enemas of hot tap water and liquid petrolatum were given, three the afternoon and evening preceding the operation and one the morning of the operation. Food and liquids were permitted until midnight preceding the day of operation. Pentobarbital sodium was given an hour before operation. Penicillin was started preoperatively one day before operation, 15,000 units every three hours.

OPERATION

Since the operation is one that requires detailed description and explanation, it accompanies this paper as a separate article. Suffice it to say that we include a block excision as the method best assuring against recurrence. If all the offending tissue is removed, postoperative sinuses and pockets are pseudorecurrences. This is in accordance with many authors, notably, Tendler,[3] Rogers and Hall,[4] Weeks and Young [5] and Barnett.[6] Kleckner [7] presented the results of the members of the American Proctologic Society and showed in a review of over 4,000 cases that open resection was least apt to result in recurrence. Lahey [8] stated, "Wide dissections and complete removal of pilonidal tracts are necessary in order to prevent recurrence of pilonidal sinus."

3. Tendler, M. J.: Pilonidal Sinus: A Review of Its Literature and a Report of 87 Cases, South. M. J. **34**:1156-1168 (Sept.) 1941.

4. Rogers, H., and Hall, M. G.: Pilonidal Sinus: Surgical Treatment and Pathologic Structure, Arch. Surg. **31**:742-766 (Nov.) 1935.

5. Weeks, R. B., and Young, G. G.: Sacrococcygeal Cyst: Report of Two Hundred Cases in an Army Hospital, Am. J. Surg. **60**:260-263 (May) 1943.

6. Barnett, L. A.: Pilonidal Cyst: The Post-Operative Problem, Am. J. Surg. **64**:338-345 (June) 1944.

7. Kleckner, M. S.: Pilonidal Sinus: Its Surgical Management, Tr. Am. Proct. Soc. **37**:166-172, 1936.

8. Lahey, F. H.: A Further Suggestion for the Operative Treatment of Pilonidal Sinuses, Surg., Gynec. & Obst. **54**:521-523 (March) 1932.

Therefore, though recurrence may occur at a later date, the importance of the surgical procedure is limited in its relationship to such a misfortune dependent mainly on the skill and experience of the operator in the extirpation of the offending tissue. We are convinced that block excision should be the method of choice best assuring freedom from recurrence, since scar and inflammation many times prevent the visualization of this epidermal tissue, much less its successful removal.

As already stated, many papers report the various means of excising pilonidal sinus and advocate many methods for varying types of involved tissue areas. Thus Rogers,[9] reviewing the cases at the Massachusetts General Hospital from 1924 to 1931, in 119 patients reported 36 per cent "recurrence" in primary suture, 50 per cent in partial closure, 18 per cent in open packed incision and 30 per cent in all combined methods. Silverman,[10] in reviewing 85 cases from 1931 to 1934 of the Jewish Hospital in Brooklyn, cited 30 per cent "recurrence" in closed operation, 26 per cent in partially closed operation, 21 per cent in open operation and an average of 25.5 per cent in all types. Kooistra,[11] in a review of 89 cases, showed permanent cure in 72 per cent, in which excision and packing, excision and partial closure, excision and closure with later pack, excision and primary closure or excision with primary closure and drain was done. Breidenbach and Wilson [12] cited excision with various types of suture, drain or packing, with 73 per cent cures. Many articles with similar results could be cited. We believe that with the recognition and acceptance of block excision, and thereby the increased likelihood of a complete removal of the pilonidal tissue, combined with a good operative closure and aided by sulfonamide and penicillin therapy much confusion concerning the type of procedure to use will be removed. Since our described method of preoperative and postoperative care combined with a closed operative procedure, described in the accompanying article, has given excellent results, we advocate its more general adoption and the sound principles of surgery which it follows. The chief point of merit lies in the fact that it is adapted to extensive pilonidal cysts in which simple primary closure fails. In addition, good reason dictated its use in the simpler cases as well as in the extensive high, low or laterally extending ramifying lesions. In this series primary closure was used in all cases,

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9. Rogers, H.: Pilonidal Sinus, Surg., Gynec. & Obst. **54**:803-810 (Dec.) 1933.

10. Silverman, I.: Pilonidal Sinus and Its Treatment, New York State J. Med. **39**:1598-1602 (Aug. 15) 1939.

11. Kooistra, H. P.: Pilonidal Sinuses, Am. J. Surg. **55**:3-17 (Jan.) 1942.

12. Breidenbach, L., and Wilson, H. L.: Pilonidal Cysts and Sinuses, Ann. Surg. **102**:455-463 (Sept.) 1935.

and in the last four months the new operative procedure was used routinely in all cases excepting 4, in which the cysts were closed by simple closure. During the latter period a total of 83 patients were operated on, 79 operations being by the new operative method. In the total series of 130 cases, all operations were by primary closure: 92 were done by the new procedure and 38 by simple closure.

Two cases not reported in this series but seen consecutively with the group of 130 cases were cases of anorectal dermal sinus, or, as might be termed with our misnomer classification, anorectal pilonidal sinus. Both these cases had associated sacrococcygeal pilonidal sinuses as discrete entities. Excision was open. They are being reported on in a separate article.

POSTOPERATIVE CARE OF THE PATIENT

Though initially penicillin was administered for four days postoperatively, before the series was half over it was given routinely, 15,000 units every three hours for eight days postoperatively. Administration of sulfadiazine and sodium bicarbonate, each in 15 grain (.97 Gm.) doses administered every four hours, carried for eight days postoperatively in the early series, was later extended to the tenth postoperative day. However, the midnight and early morning hour doses of both penicillin and sulfadiazine with the sodium bicarbonate were omitted throughout, it being believed that an uninterrupted sleep permitted a smoother-running busy ward and a happier, rested, and thereby healthier, patient. A strict nonresidue diet, avoiding milk, was used routinely through half the series and then extended to the tenth postoperative day. The exceptions to this were 2 cases of dysentery, 1 a case of proved amebic disease, the condition in both being controlled by antiamebic treatment. Bowel movement was allowed to come of its own accord, without need or resort to enemas, when all medication was stopped on the tenth day and a soft diet was started. As an almost invariable rule, no bowel urge occurred until this period. The patient was not encouraged to go to stool until bowel urge necessitated and was not allowed out of bed until then. A young, vigorous age group permitted this strict regimen. Surprisingly little loss of weight occurred, and this was quickly regained. No ill effects were encountered. Possibly patients in whom the lesion was complicated with cardiorenal disease or other patients should have this interval of time shortened.

RESULTS

The evaluation of the surgical results of this type of treatment and management requires first an acceptance of certain basic facts.

First, it must be realized that with the military, in rather pronounced contradistinction to the usual civilian status, a healed wound

means a wound ready to stand all the vigorous strain and abuse that ordinarily is not required in civilian life. Away from hospital centers, a slight complaint, in the eyes of a pharmacist's mate, may assume enough significance to seem a grave condition. Thus, a small break in the skin, with its moisture and seepage, or a minute postoperative sinus is a "recurrence" in the eyes of both the patient and his young and inexperienced medical counselor. When this occurs, another physician, not thoroughly conversant with the subject, is also apt to probe and incise in the attempt to diagnose or perhaps variously treat a condition best left alone. Consequently, differing from private practice, hospitalization is necessary until no further medical care is necessary and healing is complete to the last portion of epithelium.

An unfortunate, disturbing and in some ways somewhat ludicrous occurrence was periodically reported. Some patients from overseas or in line for overseas duty would maliciously attempt to break open their incisions or produce postoperative sinuses. "Bed bouncers" were reported generally but were specifically named only rarely. Occasional broken wire sutures attested to at least overactivity on the part of patients in bed. For these and other reasons it is our belief that even better results, with fewer complications, will be obtained in civilian practice.

Naturally, an operation that leaves an excellent protective pad of tissue, that no type of open operative operation can profess to do, is necessary for most military personnel. A successful closed operative procedure obtains a good tissue covering in an otherwise poorly protected area over the sacrum. The new operative procedure offers more.

Time is an urgent factor in military medicine. The Navy's slogan, "As many men, at as many guns, as many days as possible," was ever foremost in our minds. For this reason more than any other, a short period of convalescence was a vital necessity. Overcrowded wards and a hospital operating beyond capacity likewise demanded it. Though patients returned to duty in some cases too soon after operation, the majority were returned in about three weeks, the average number of postoperative days of treatment in the group without complications being seventeen and one half. It is our opinion that a good rule to follow in a normally healing closed procedure is to keep such patients in the surgical ward, with no outside liberty for fifteen to sixteen days postoperatively, and to arrange their discharge to permit full duty no sooner than three weeks postoperatively. On reflection, this seems logical, since eighteen to twenty-one days is the normal period necessary for fairly complete reparative healing changes to occur in any wound and it is a well known fact that further fibrous healing change occurs even after that period. The acts of sitting and walking subject the healed wound to more strain than wounds from most operations. The anatomic

configuration, with the natal crease and gluteal folds, and the spreading strain and tension coincident to the mere act of leg movement and sitting require a solid wound.

We do not believe that in civilian practice it is necessary to keep the patient with the uncomplicated wound in the hospital over two weeks postoperatively. Furthermore, small breaks in the skin that required a longer postoperative management in the United States Naval Hospital should be of no concern in civilian practice and in most instances should not require further hospitalization, as was true in this series.

With these facts in mind, we reasoned on this basis: that the cases without complications in this series of 130 cases should include those requiring no more than thirty days of postoperative care, particularly as this group, besides the cases of perfectly healed wounds, included only cases of cutaneous irritation and superficial, small breaks in the skin that healed readily. This group consisted of 108 cases, or 83 per cent of uncomplicated conditions in the series of 130. The patients required an average postoperative care of only seventeen and one-half days.

THE GROUP OF CASES WITH COMPLICATIONS

In this group we classed all cases in which, by reason of infection and tissue break, the patients required treatment over thirty days. These numbered 22 cases. In 1 case, a recurrent lesion required reoperation and is not included as a complication. The therapy is listed as a failure. However, operative healing was complete except for a persisting sinus. This constituted 16.9 per cent of the total series.

Simple closures applied to the cases of simpler operation in the early part of the series, until discarded almost entirely in the later half, had a higher incidence of complication, eight of the thirty-eight simple closures, or 21 per cent, being complicated. The new operative closure showed relatively fewer complications, fourteen out of ninety-two such closures, or 15.2 per cent, being complicated. When the fact is considered that this new operation was applied in many cases of severe degree, with extensive involvement, in which the usual simple closure was impossible, the merit of the operation itself is more obvious. When the number of postoperative days of care necessary is compared, the complicated simple closure required 55.1 days of average care as compared with 44.6 days in the complicated new operative procedure. An analysis of the individual complicated cases of simple closure demonstrated the reason as due to results in 3 of the 8 cases. The lesions separated down to the base of the wound, with a subsequent need of ninety-seven, sixty-two and fifty-eight days of postoperative care. All complications with the new operative procedure were breaks of the superficial structure of the wound, which, though in some instances

were accompanied with infection and hemorrhage in the deeper portion, healed with greater rapidity. It is evident, therefore, that the advantages of the new operation under identical conditions of management and care were fewer complications and requirement of less time to heal.

CARE IN THE CASE OF COMPLICATION; ITS PREVENTION

As already stated, the greatest difficulty experienced was in the prevention of breaks in the skin. Experience has shown that the silk suture of the skin is preferably left intact until the tenth postoperative day. Great care must also be taken in exposure of the wound. The adhesive tape should be cut at the side of the dressing and turned back rather than peeled off. If stitch abscess or infection is present, lateral tension may further separate. Adjacent sutures may sometimes be left intact for another several days to prevent further separation of the skin. Since this stage of superficial or deeper infection has weakened the tissue to a varying degree, the supporting action of the adhesive dressing is even more necessary. Though early treatment with irrigations, dry heat and open air is many times highly desirable, it should be postponed for a few days, until the wound is more solid. Frequently, daily or twice daily dressings must also be reapplied, the dressing must be mounded so as to secure anterior-posterior downward pressure and great care must be given to the adhesive straps, which are carried anteriorly over the anterior iliac crest and abdominal wall, new adhesive tape being placed over the old, original straps. When conditions permitted, various methods to overcome infection were used, viz., irrigation of cavities with 1 : 6,600 chloroazodin and cleansing with isotonic solution of sodium chloride with aqueous merthiolate, 70 per cent alcohol and such. Infra-red lamp therapy was used as soon as the wound could be left open. Sitz baths were later used when desirable and when solidity of tissue and the degree of healing permitted.

Hot weather, perspiration and macerated skin were particularly difficult factors in that a phagedenic infection with hemolytic streptococci and Bacillus pyocyaneus was apt to occur. Anaerobic infection in such circumstances was more prone to occur, since the compression bandage excluded air. The proximity of the anus was a menace, particularly when the wound by necessity carried into the substance of the anal margin and involved the external subcutaneous sphincter. It was necessary to excise skin margins in such circumstances and to treat them with hydrogen peroxide and zinc peroxide paste. The resultant open area was usually depressed, was slow in forming granulations and was indolent. Six patients with cysts in this stage were treated by an excision of this ulcer and suture, penicillin being used by instillation and hypodermic injection for four to six days. Five cysts healed by primary

intention and one rapidly in spite of only a partially successful skin closure. Removal of heavy scar was responsible for the success of this skin closure. Such secondary closures of the skin should undoubtedly have been resorted to in other cases as part of an early routine in such minor complications.

Small postoperative sinuses were treated in the last few weeks of this series by the injection of a modified Carnoy solution, as described by Cutler and Zollinger,[13] after all acute inflammation had subsided. It also was a method that should have been used routinely, since it was found highly successful; two or three injections every one to three days alone sufficed to secure solid healing. The solution was prepared according to the following formula.

Absolute alcohol	6 cc.
Chloroform	3 cc.
Glacial acetic acid	1 cc.
Ferric chloride	1 Gm.

THE SEVERELY ABSCESSED AND INFECTED WOUND

Such a complication as severe abscess and infection in the simple closure resulted in wounds difficult to heal and in 3 cases, as already stated, changed the closed wound into one widely separated, resembling an open block excision type of wound after infection and cutaneous necrosis had subsided.

In cases in which such severe infections occurred in the new type of operation, the deeper structures and muscular layer remained intact and healing was relatively rapid. In consequence, a good covering of tissue was still present over the sacrococcygeal region, a result highly desirable, since the operation aimed for not only rapid healing but a good protective pad of tissue. Frequent dressings, prolonged use of adhesive binding, sitz baths when permissible, infra-red lamp therapy and irrigations with isotonic solution of sodium chloride and 1 : 6,600 chloroazodin, and, of course, a temporary additional course of penicillin were the chief additional adjuncts of therapy.

COMMENT

Whereas it is apparent that no single operative procedure can in itself alone be responsible for a cure of this condition, it is apparent that the operation in itself is largely responsible for the successful outcome, especially when the success of the outcome is judged in terms of hospitalization and care necessary for cure. When judgment is also directed to the type and quality of the postoperative wound, emphasis is again more properly directed to the importance of the operation in determining the excellence, or otherwise, in the securing of the result. Certainly some operative cures do not result in satisfactorily protected

13. Cutler, E. C., and Zollinger, R.: The Use of Sclerosing Solutions in the Treatment of Cysts and Fistulae, Am. J. Surg. **19**:411-418 (March) 1933.

areas but, as in an open block excision, are subject to criticism in the retracted, denuded and scarred site of healed sacral or sacrococcygeal exposure. Sulfonamide therapy is certainly a requisite in aiding the successful outcome of what could otherwise be an unsuccessful procedure. Likewise, penicillin therapy must be of aid in combating strains of streptococci that might otherwise prove disastrous. One of us had resort to this new operative procedure, with varying fair to excellent results, before penicillin was available. The excellent results in the simple closed procedure by Kennard, as previously mentioned, show that penicillin is not an absolute requisite.

It seems only logical to assume, however, that all points concerned in the careful preoperative and postoperative care and treatment of these patients must be of importance in securing a rapid and successful surgical cure and normal functioning anatomic part.

Emphasis is also given to the important fact that all 130 patients were surgically discharged as healed. Recurrences are, of course, possible if any pilonidal tissue remains. It has been found impossible to follow these cases for future check-up. On the basis that a block excision has had no known recurrences in some 42 cases in the private practice of one of us, it is at least hoped that such is true in this series. The 1 case of a known recurrent lesion typifies, however, the impossibility of being surgically perfect.

That the new operative procedure is one that should be used routinely seems apparent because of the eventual good result in spite of complications and also because of the further reduction in the incidence of complications. The accompanying table clearly demonstrates the point in question.

Results of Operation on Pilonidal Cysts

	Number of Cases and Percentage of Total Series		Number of Cases of Uncomplicated Cysts and per Cent of Group		Average Number of Days of Treatment of Uncomplicated Cysts	Number of Cases of Complicated Cysts and Percentage of Group		Average Number of Days of Treatment of Complicated Cysts
	No.	Per Cent	No.	Per Cent		No.	Per Cent	
New operative procedure.....	92	70.7	78	84.8	17.4	14	15.2	44.7
Simple closure procedure.....	38	29.2	30	78.9	17.6	8	21.0	55.1
Total.....	130*	100	108	83.0	17.5	22	16.9	48.5

* One additional case should be listed as "failure" due to incomplete excision.

We believe that in civilian practice, with more time taken in the preparation of the patients so as to obtain a totally quiescent lesion, complications would show an extremely low figure and the rapidity of healing and convalescence would be further improved.

CONCLUSIONS

1. A review is given of 130 consecutive cases of inflamed pilonidal sinus, with a combined type of operative management and a new operative closed procedure.

2. Part of this series was a control group in which a simple operative closure was used.

3. Penicillin and sulfonamide therapy was used as a successful adjunct.

4. The careful preoperative and postoperative care is given, and treatment to avoid as well as to treat complications is described.

5. The advantages of the new operative procedure seem demonstrated by the lowered incidence of complications, for the greater part minor.

6. Complete healing occurred in all cases.

7. Future recurrence depends entirely on pilonidal epithelial remnants being left but is likely to have a low incidence, since block excision preceded closure in all cases.

8. The operative procedure is given detailed description in the accompanying article.

NEW AND SUCCESSFUL CLOSED OPERATIVE PROCEDURE FOR PILONIDAL SINUS

Gluteus Maximus Mobilization: A Sliding Muscle Graft Procedure

COMMANDER CHARLES E. POPE (MC) U.S.N.R.

THE operation explained in this paper, a sliding gluteal muscle graft, has gradually evolved to its present completed state, commencing in 1942 to 1943 at the United States Naval Hospital, Mare Island, Calif., where I first devised and used it. Initially used as a closed procedure when the extensive involvement of tissue prevented closure by any other means, the merits of the procedure and its improvements finally permitted its use in all cases.

The purpose of this article is to describe the technical details of the operation and the surgical principles it entails. A combined method of management of pilonidal sinus and a review of ninety-two successful operations demonstrating its applicability accompany as a separate article. It is, therefore, no hurried judgment that asks for counsel, and, though improvements may yet occur, I believe that no considerable change is indicated.

Numerous articles describing various operations for pilonidal sinus group them roughly into three groups, that is, open operations, closed operations and partial closures. The last may be said to include the closure type with drainage and also the types which in several ways marsupialize the wound, primarily for the purpose of more rapid healing. It may also be stated that since the advent of sulfonamide therapy and penicillin therapy a large number of papers have advocated a closed procedure, particularly since military surgical procedures drew close attention to the prevalence of pilonidal sinus in the young age group. It is immediately evident that a certain number of methods and procedures accepted in the past can be discarded or at least considerably modified in view of this advance in therapy. It is also evident that a closed procedure is not in itself a new procedure, since in many centers it is used successfully. Certain definite failings, however, are manifest in the usual closed or partially closed procedure.

In the first place, since most excisions expose the sacral fascia, a relatively avascular area of tissue is present, showing, therefore, poor

Dr. Emile F. Holman, Dr. Henry W. Hudson, Dr. H. S. Kennard and my commanding officers at the United States naval hospitals, Mare Island, Calif., and Chelsea, Mass., gave professional courtesies, encouragement and helpful advice.

healing qualities. Coaptation of tissue over this area is usually by a layer of subcutaneous fat and overlying skin, a combination prone to infection, and a dead space poorly filled and prone to the accumulation of serous or sanguineous exudate.

Closed procedures are limited in their applicability, since frequently, and especially with an extensive pilonidal sinus, closure is under undue tension. As a result, such closures effected are liable to failure due to early postoperative splitting, infection, hemorrhage or tissue necrosis. When technically impossible to effect the closure, recourse is had to partial closures or drainage types of procedure or else an open wound is left, necessitating a prolonged period of healing. Such procedures, especially the open type and those marsupializing the wound, leave a healed wound that has much to be desired, since an inadequate covering is left over the denuded sacrococcygeal region. Not only is the last stage of such healing often particularly difficult to attain, but strenuous physical activity must be avoided during the many weeks of healing. Because of the vulnerability of the area, it is prone to injury and not infrequently remains sensitive. In military life it does not seem the best way of dealing with the condition, and, in fact, most authors are now agreed that the open operation in military life should be outlawed. One such lesion seen at the United States Naval Hospital, Mare Island, Calif., remained unhealed seven months after operation and several two to three months or more following the open procedure.

The new operation, involving mobilization of the gluteus maximus muscle, successfully overcomes the numerous disadvantages of other types of pilonidal operations, whether they be closed, open or partially closed. The advantages of a muscle operation occurred to Ottenheimer,[1] but the operation was not attempted. In discussing the difficulty in healing due to faulty obliteration of dead space at operation, he stated, "Delayed dead space formation might be avoided if we could successfully interpose muscle between fat and bone to afford a resilient base for the scar in the fat. It might be possible to turn into the cavity, for example, two butterfly wings of gluteus muscle, one from either side."

Hipsley [2] unsuccessfully attempted this method suggested by Ottenheimer, reporting 6 cases in which a gluteus maximus flap was drawn subcutaneously into the wound and primary closure attempted. Complications due primarily to bleeding occurred, but, though the wounds became open, healing by reason of the vascularity of the muscle and obliteration of faulty dead space was exceedingly rapid. Hipsley therefore stated the belief that the method was well worth modification, improvement and further trial.

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1. Ottenheimer, E. J.: Pilonidal Sinus, Am. J. Surg. **2**:120-122 (July) 1933.

2. Hipsley, R. W.: An Operation for Pilonidal Sinuses, Am. J. Surg. **63**: 357-361 (March) 1944.

Similarly, Miscall and Holder [3] also reported an operative procedure, with closure, by the turning of bilateral musculofascial flaps of gluteus muscles onto the sacrococcygeal fascia surface and the suturing of all tissue layers in the midline. Their operation lays fascia against fascia and requires wide block excision to expose the gluteus muscles for subsequent flap dissection. Mobilization of tissues to secure freedom from tension requires further lateral incision, both subcutaneously and intramuscularly, to cover the defect from wide block excision, technically necessary. They report 22 cases in which results were successful, with rapid healing and short hospitalization.

As will be seen, both operations differ materially from the sliding muscle graft, to be described, and are technically more difficult to perform.

Since the usual or modified closed procedure inadequately closes a dead space or is under undue tension and in many instances cannot be successfully performed, a gluteus maximus muscle mobilization was devised, with the following merits: (1) adequate replacement of dead space by a muscle-sliding graft; (2) freedom from tissue tension by muscle mobilization; (3) increased blood supply, increased rapidity of tissue healing and enhanced ability to combat infection by reason of the muscle graft and supple tissues, free from tension; (4) a more adequate protective pad of tissue covering an exposed defect in an otherwise relatively avascular area, where exposed sacrococcygeal bone and fascia require protection; (5) a greatly increased therapeutic effect from sulfonamide and penicillin therapy by the blood stream route, for obvious reasons; (6) a procedure adapted to all cases excepting those in which, rarely, spinal or bone involvement occurs, and (7) the permission of a block excision, which has been recognized as least apt to leave offending tissue and to allow subsequent recurrence.

No operation known is free from complications. Operative complications are more frequent in the infected condition and are applicable to infected pilonidal sinus. Consequently, the operation is best performed after infection has subsided, and the longer the period following the initial incision, drainage and inflammatory changes, the less chance for postoperative infection, complications and resultant failure. A combined method of treatment should always be conducted and great care directed toward even apparently minor details, which otherwise may cause a rapidly increasing hazard through their neglect or omission. Since detailed facts in the combined method of manage-

3. Miscall, L., and Holder, J. E.: Pilonidal Sinus: A Method of Closure by Musculo-Fascial Flaps, Mil. Surgeon **93**:457-461 (Dec.) 1943.

ment of cases have already been covered in the accompanying paper, these will not be enlarged on.

That the series of one hundred and thirty operations should have shown fewer complications bears mention. So many patients were seen, so overcrowded were the wards and so crowded to capacity was the operating room schedule that the practical solution seemed to be in operation on the inflamed sinus before complete resolution had occurred. That good results were obtained in spite of an occasionally contaminated field of operation speaks well for the procedure, even though far from flattering to the operator.

Recurrence may be experienced in some cases, since 1 case of a known recurrent lesion is included in the series and one cannot profess perfection. Since block excision and the open method used in private practice were highly successful in allowing no known recurrence in a series of over 40 cases, this series should have a low incidence, block excision having preceded the surgical operation of closure. It is unfortunate that a follow-up is impossible in this series. It was attempted in the early cases of operation at the United States Naval Hospital, Mare Island, Calif., and was found impossible to obtain.

THE PRINCIPLES OF OPERATION

To accomplish healing by first intention, it is important that the involved tissue is handled with care not only to avoid trauma but likewise to avoid contamination, since many of the cases show buried infection in the depth of scar tissue which probing and incision do not always demonstrate preoperatively. Bleeding must be properly controlled, but a minimum of hemostatic sutures is desirable, since the less foreign substance incorporated in a wound potentially or definitely infected, the better the outcome. Undue tension of the tissue should be averted by avoidance of tight suture, whether retention, skin or mattress suture, and yet a careful approximation of all tissue layers must be obtained. Above all is the need for the obliteration of all dead space. The operation demands these requisites, so necessary to all good surgical treatment. Disregard of these necessary surgical principles is apt to result in failure or complications, which is not strange when one remembers that before the use of sulfonamide drugs and penicillin to close such lesions was many times contrary to good surgical judgment. Careful bandaging and care are likewise necessary postoperatively, with bed rest, bowel movements being prevented before healing is complete so as to avoid soiling and contamination and preventing the trauma that might otherwise occur.

The operation was performed in 92 cases. Thirty-eight simple closures were likewise done, which served as a control series. The operation was finally adopted as a routine procedure in all cases.

THE BLOCK INCISION

The block incision, the preliminary and initial step, is highly important in that complete excision of all offending pilonidal tissue is necessary to assure against recurrence. It must be done neatly and with painstaking care, so that exacting coaptation of tissue may later follow.

The patient is preferably placed in reverse Trendelenburg position, with side straps of adhesive tape to withdraw the upper part of the buttocks for better exposure. This method, originated by Bearse, is exceedingly helpful. Care should be taken that the straps are well beyond the field of operation so that later contamination may not occur.

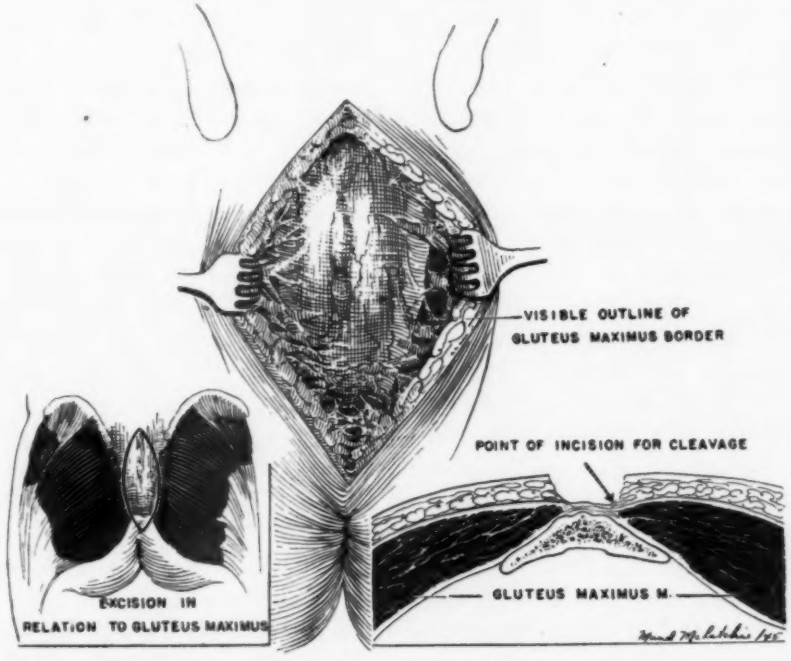

Fig. 1.—Semischematic illustration demonstrating block excision of pilonidal sinus.

In preparation of the field for operation, antiseptic is used on the adhesive tape but contact of the tape with both ether and alcohol is avoided.

The previously prepared field of operation is now cleansed with ether, followed by merthiolate. The anus has previously been covered with a wedge of gauze between the buttocks to protect its surface and to wall it off from the field of operation.

The incision is usually elliptic, is made at right angles to the cutaneous surface on its rolling plane and carries well beyond the point of tissue involvement in the sacrococcygeal area. The points of the ellipse

should always be in the median raphe. The location is determined by careful probing of the sinus and by palpation in advance of the incision. Symmetry of its sides is desirable but not entirely necessary or always possible, when lateral extension forbids. Lateral extension requires at times a lateral Y for lateral closure of the ellipse. The zone of incision is aided by a light marking on the skin with the back of the blade or the point of the scalpel. Care must be taken that the sinus does not contaminate the gloves, the scalpel or the instruments.

The skin scalpel is discarded. The upper pole is grasped with an Ochsner or Kocher clamp, and, with a new scalpel, the incision is carried on the top and adjacent sides through fat to sacral fascia. Almost invariably it will be found necessary to carry to this depth. The side incisions should not carry laterally outward but preferably slightly saucerize by medial direction. A sweeping incision by the scalpel strips the raised block of tissue from the sacral fascia and when necessary includes an outer layer surface of its substance. The swinging of the elevated tissue from side to side permits good symmetry of excision, avoids incision of the cyst and tracts and permits a desirable smoothness of procedure. As the lower pole is approached, care must be exerted first to carry the excision close to and carefully over the coccyx, so that, when not necessary to excise, the anococcygeal ligament remains intact. Low extending tracts require care in their excision so as to avoid injury to the posterior part of the rectum, levator musculature and anus. This excision of the lower pole is materially aided by the exertion of more traction once the lateral incision has carried deeply enough beyond the coccyx, for, by so doing, one finds that the fat will peel away without the need of deep incision. This avoids too deep a sulcus wound in closure.

During the block excision, clamping of bleeding vessels impedes the procedure and is to be avoided when possible until the block of tissue has been removed. Frequent sponging is necessary, but, for fear of contamination, each sponge is thrown away as rapidly as used. It is usually possible to determine the deep scarred limits of the tract, visible as a rule on the under surface of the elevated block. Careful scrutiny of both the wound and the specimen removed is necessary, and suspicious areas should be removed. When the tract is cut inadvertently, a reexcision should go beyond the point or area of tissue error, a new scalpel being used and the old discarded. The excised block of tissue may be incised and examined if handled so as not to invite contamination.

A Y extension beyond the sacral fascia anatomically carries over the gluteus or occurs perianally, permitting closure as a simple problem, since there is no dead space as is found in the sacrococcygeal region. Such lateral Y tract wounds have an adequate blood supply and may have muscle at their depths. If pilonidal sinuses were solely confined to

such areas, no surgical problem of moment would exist. The extension usually is the extension of the inflammation rather than that of the pilonidal tissue. Its excision, however, precludes the possibility of leaving pilonidal tissue occasionally present in wide lateral or downward extensions. Excision is necessary also to secure good aseptic closure. Therefore, excision rather than incision should be done.

Since a hot isotonic solution of sodium chloride is used both now and later to control bleeding, it will be found possible to use fewer surgical gut ligatures. These should be a figure of eight suture ligature, mass ligature being carefully avoided, with no. 00 plain surgical gut, thought the most desirable, so as to avoid excessive or unnecessary foreign body reaction.

THE GLUTEUS MAXIMUS CLEAVAGE MOBILIZATION

Experience has shown that a single side of gluteus mobilization in practically all cases suffices to mobilize the widest areas of lateral excision.

The gluteus maximus muscle is attached to the lateral surface of the sacrum and coccyx, its posterior surface curving backward in a plane raised beyond the posterior surface of the sacrum. From this area of attachment its fibers fan superiorly slightly upward, in midsacrum laterally and in the sacrococcygeal lower pole in a slightly downward direction. Its strong fascial covering fuses with the sacral and sacrococcygeal fascia. On the side desired, the outer layer of muscle is disengaged from this attachment. The side oposite the area of lateral extension may be most desirable. The adhesive ties now should be disengaged from attachment to the operating table to facilitate the cleavage. A plane of muscle tissue, with its superimposed and attached fascia, subcutaneous fat and skin overlying, is obtained by muscle cleavage separation through forcible blunt lateral dissection. In detail, this is done as follows:

The base of the wound is carefully palpated to determine the rolling edge of sacrum and the gluteus attachment. The scalpel, held carefully, cuts muscle and fascia at this edge from top to bottom, following the rounded curve of sacrum and coccyx in the superior-inferior as well as in the anteroposterior plane. An equidistant depth of muscle thickness is obtained approximately half through the muscle. A smooth stroke of the scalpel prevents a ragged edge of muscle or torn fascia, which would be undesirable. The insertion of the operating fingers then permits by forcible lateral and upward and downward extension a blunt cleavage separation that is relatively bloodless. This may be carried as far laterally as is necessary for supple closure of the wound. In general, one and one-half times the size of the base of the wound

is found to be the required distance of lateral cleavage. Usually a further small incision of the lower gluteal fibers at the ligamentous attachment at the lower coccyx level is now necessary so that the full cleavage mobilization may be realized.

Bleeding occurs momentarily and profusely from arteries of the sacral muscle bed, in which a smooth cuff of muscle tissue is allowed

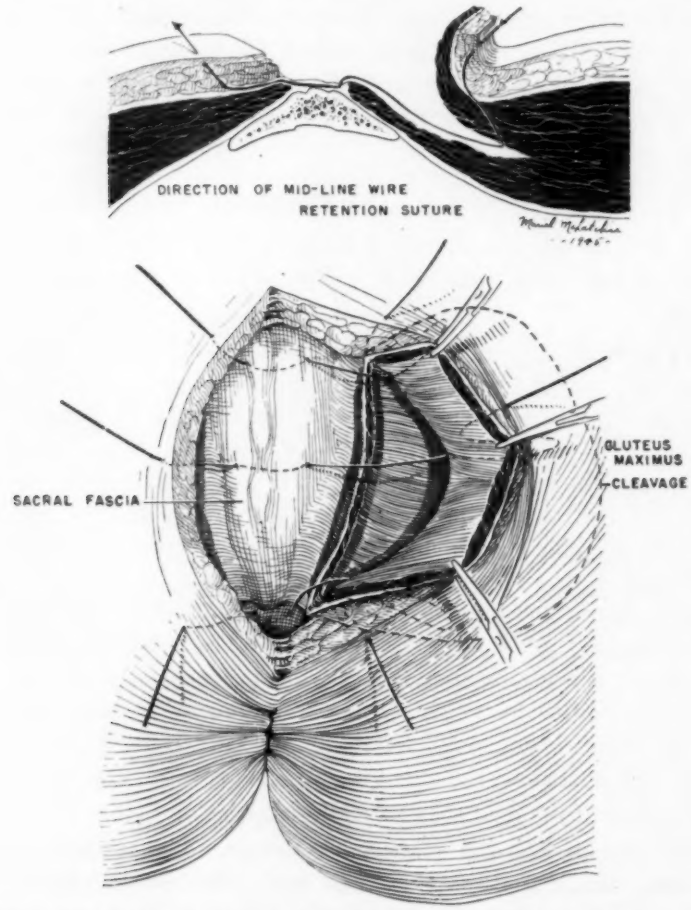

Fig. 2.—Semischematic illustration of a gluteus maximus cleavage and the insertion of midline wire retention sutures.

to remain. Since bleeding usually stops in a minute or so, it facilitates the procedure to ignore it until the cleavage mobilization is completed and then, and only then, to suture with plain 00 surgical gut. Lateral muscle incision, formerly used instead of cleavage, causes bleeding which is difficult to secure in the depths of the muscle tissue and should be avoided. The usual spontaneous cessation of muscle bleeding when

incision and lateral cleavage are done correctly is spectacular in view of the preceding profuse flow.

The operator will be both pleased and somewhat amazed at the easy closure now possible to effect. It is possible not only to cover the whole sacral and coccygeal area with a firm sliding layer of muscle tissue, with its overlying skin and fat, but also to make the closure supple and free from tension. Sulfanilamide is now frosted in the wound and gently mixed throughout. Excepting for the skin and its sub-

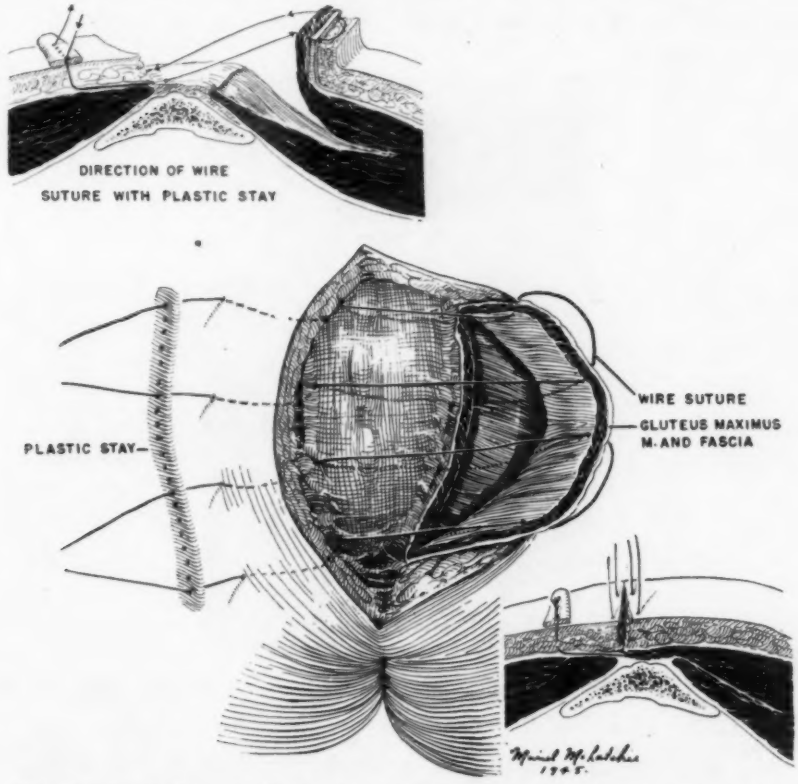

Fig. 3.—Semischematic illustration of the insertion of wire mattress sutures to a sliding gluteus maximus graft and illustration of a completed supple closure.

cutaneous layer of fat, closure is effected solely by wire suture. Two sets of wire sutures are used.

Three wire retention sutures and occasionally, in long wounds, a fourth are used to secure a moderate anterior-posterior pressure in the midline wound. These, equidistantly placed, carry through skin and fat from either side and carry through sacral fascia in the midportion of the wound. The lowermost of these wire sutures in the lower pole of the wound catches skin and fat but, being below the coccyx and its

fascia as well as the gluteus muscle, carries through the bottom layer of wound sulcus, close to the posterior wall of the rectum. On the side where muscle cleavage has occurred, it is necessary that the suture carry laterally through subcutaneous fat to enter the mobilized muscle layer at its point of most lateral cleavage or else, on tying and tension, an inadequate covering of muscle will result across the base of the sacrococcygeal fascia. These wires are tied over five or six layers of folded gauze in the midline. To avoid undue tension and pressure, a three-fourths length tongue depressor placed lengthwise in the gauze distributes pressure on the sutured skin over the flat surface of the posterior sacrum.

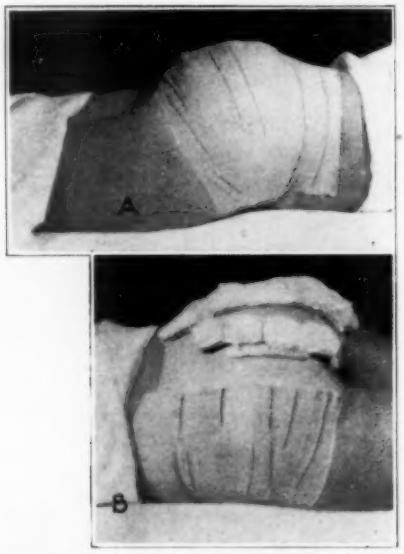

Fig. 4.—*A*, pilonidal sinus, with adhesive dressing. *B*, pilonidal sinus, with the dressing exposed.

The other set of wire sutures carries through the mobilized muscle and its fascia close to its edge. The ends of each mattress suture carry to the base of the opposite intact gluteus muscle to carry out beyond the first set of sutures through subcutaneous fat and skin.

I devised a plastic lucite stay, molded to conform to the average outer curve of the buttocks, through which these wires insert and tie. These measure ¾ inch (2 cm.) in width and 5 inches (12.7 cm.) in length and are smooth and rounded, with a slight bend at the ends so as to fit smoothly and not dig into the skin. Holes, bored about wire size, are placed ¼ inch (0.6 cm.) apart in the midline throughout their length. Two mattress sutures, with the four wire ends placed evenly on this plastic lucite stay, work excellently and

prevent trouble experienced before in undue cutaneous pressure, blistering or necrosis. Care must be taken, of course, that undue tension does not occur in tying.

The skin is closed with no. 10 silk, a deep vertical mattress suture being taken. In addition, it is important to use interrupted skin sutures as well, so no shift of skin can later occur.

The dressing is mounded slightly, an A.B.D. pad is cut to cover the wound neatly and an adhesive moderate pressure bandaging is applied. It is important that these strips be carried over the anterior iliac crests and that the buttocks be carefully and smoothly bound for

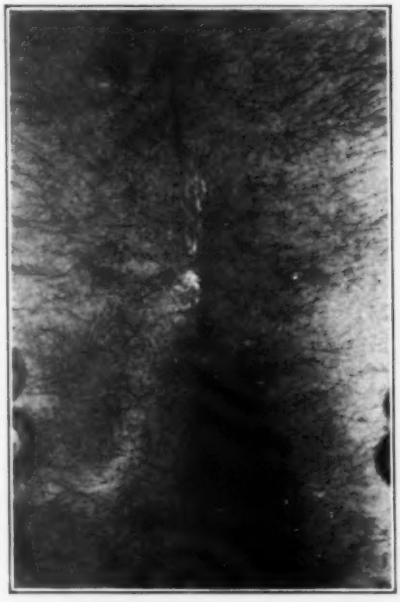

Fig. 5.—Pilonidal sinus, showing a healed operative wound.

protection of wounds, pressure on wounds and partial immobilization of the muscle.

No subsequent dressings are necessary until the eighth day, when the wire sutures are removed with care. The skin sutures are removed on the tenth postoperative day. Continued adhesive binding of the wound is preferable to prevent undue strain and trauma until the fifteenth or sixteenth day. After the tenth day, gradually increased activity is permitted.

Though I have formerly used a bilateral gluteus maximus cleavage in a fair series of operations, only two were done in this series of ninety-two, and these were not necessary. Either side may be used, regardless of the pathologic changes present. In this series eighty-

three cleavages were of the right gluteus maximus muscle, mainly because it was more convenient when operating on the left side of the patient to do so. In 7 cases cleavages of the left gluteus maximus muscle were used.

It should be mentioned that a slight sensory numbness of tissue may be experienced for a few weeks in some cases. This gradually disappears. Care, of course, must be taken not to cut down onto the bony part of the sacrum but, as described, to leave a small cuff of muscle tissue along its lateral border.

This operation was also found applicable in certain orthopedic cases, and a paper describing its use in such instances is now in the process of publication.

CONCLUSIONS

1. A new and successful operation for pilonidal sinus is described. Block excision is done. A sliding muscle graft is obtained by gluteus maximus cleavage mobilization. This permits supple closure of all tissues and freedom from tension on tissues.

2. The operation has further merits in that it adequately fills all dead tissue space with muscle substance, is conducive of rapid healing, offers an excellent protective pad of tissue and is performed with ease.

3. The operation follows sound principles of surgical treatment.

4. In a series of one hundred and thirty closed operations, ninety-two gluteus maximus sliding grafts were successfully performed. The remaining thirty-eight simple closure operations served as a control series. The results of this series and a detailed regimen for their management are described in an accompanying paper. The results of this series further substantiate its claims for adoption.

5. The operation is applicable in all cases of pilonidal sinus excepting those in which involvement of the spine or bones is shown. The technic used in extensive involvement is described.

6. The operation is applicable to certain orthopedic problems.

Evanston, Ill.

ANAPHYLAXIS-LIKE REACTIONS PRODUCED BY ASCARIS EXTRACTS

II. The Mechanism of the Shock Induced in Dogs

M. ROCHA e SILVA and A. GRAÑA
SAO PAULO, BRAZIL

IT is a well known fact that leukopenia and thrombopenia regularly accompany anaphylactic shock in every species of animals.[1] In 1924 Webb [2] made an extensive study of the leukopenia which occurs in sensitized dogs as a consequence of the injection of the antigen. Recently, Kopeloff and associates [3] and Kinsell and co-workers [4] have shown that a decrease in platelets is definitely proportionate to the gravity of the anaphylactic shock in monkeys and rabbits. They have also postulated that a rupture of those hematologic elements might help to explain the liberation of histamine, since rabbit platelets are especially rich in histamine.[5] In the case of dogs, however, it is not so easy to explain the increase of histamine in the blood as a consequence of an explosion of platelets, since those elements are very poor carriers of histamine in this species of animal. Moreover, it has been proved that most of the histamine which appears in the circulating blood during anaphylactic shock in dogs comes from the liver. This organ loses considerable amounts of histamine after in vivo anaphylactic shock, as shown by Dragstedt and associates.[6] Drastic reductions in total liver histamine in the anaphylaxis-like reaction produced by ascaris extracts were also shown in the preceding paper.[7]

From the Department of Biochemistry and Pharmacodynamics, Instituto Biologico.

1. Achard, C., and Aynaud, M.: Compt. rend. Soc. de biol. **67**:83, 1909. Behring, E., cited by Quick, A.: The Hemorrhagic Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942. Pardi, U.: Arch. ital. de biol. **64**:89, 1915. Lee, R. I., and Vincent, B.: J. M. Research **32**:445, 1915.

2. Webb, R. A.: J. Path. & Bact. **27**:79, 1924.

3. Kopeloff, N., and Kopeloff, L. M.: J. Immunol. **40**:471, 1941.

4. Kinsell, L. W.; Kopeloff, L. M.; Zwemer, R. L., and Kopeloff, N.: J. Immunol. **42**:35, 1941.

5. Minard, D.: Am. J. Physiol. **132**:327, 1941. Zion, L.; Ceder, E. T., and Crigler, C. W.: Pub. Health Rep. **54**:1978, 1939.

6. Ojers, G.; Holmes, C. A., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **73**:33, 1941.

7. Rocha e Silva, M., and Graña, A.: Anaphylaxis-Like Reactions Produced by Ascaris Extracts: I. The Changes in the Histamine Content and the Coagulability of the Blood in Guinea Pigs and in Dogs, Arch. Surg. **52**:523 (May) 1946.

There is another common occurrence in anaphylactic shock in every species of animal that merits consideration when one is dealing with the mechanism of the shock: the explosive liberation of heparin from cells to plasma. The discharges of heparin and histamine are so intimately correlated that one is induced to attribute both phenomena to a single working factor.

That a rapid disappearance of leukocytes and platelets from the circulation is not enough to explain shock is shown by the fact that liver glycogen is very effective in producing drastic reductions in leukocyte and platelet counts without any sign of circulatory impairment, as shown in this paper concerning dogs and in a separate paper concerning rabbits.[8] The final solution of the problem of anaphylaxis will probably be found in a recognition of the relative and specific importance of each one of the phenomena previously mentioned, as suggested by the experiments presented in the following paragraphs.

In the present paper we aim to analyze further the anaphylaxis-like shock produced in dogs by the injection of extracts derived from Ascaris lumbricoides. The favorable condition which induces one to study more thoroughly this particular kind of shock is the fact that it develops with extreme severity in almost all the dogs submitted to the experiment, while severe anaphylactic shock induced by a previous preparation of the animal with foreign proteins occurs only in a relatively small percentage of animals (about 30 per cent). We have reasons to believe that the presence of a macromolecular glycogen-like substance in the ascaris extracts is the factor which aggravates the condition.

EXPERIMENTAL STUDIES

The preparation of the crude ascaris extracts used in the experiments to be presented was made according to the procedure described in the previous paper.[7] Glycogen was prepared by grinding in a meat chopper the liver of a well fed dog. The mass of ground liver was treated with an equal volume of 10 per cent trichloroacetic acid solution and the mixture stirred for two hours at room temperature. After filtration, the opalescent filtrate was treated with an equal volume of ethyl alcohol and the precipitated glycogen material collected by centrifugation. The crude product was further purified by two or three redissolutions in isotonic solution of sodium chloride and reprecipitations with 50 per cent ethyl alcohol. For injection, the glycogen was dissolved in isotonic solution of sodium chloride in the proportion of 1 Gm. per 3 cc. of saline solution.

The trypsin used in the experiments of liver perfusion was an active crystalline material from Lehn and Fink Laboratories.[9]

For recording blood pressure of the carotid artery the animals were anesthesized with dial and morphine sulfate. The doses of anesthetics and the conditions of collecting samples of blood were the same as those in the previous paper.[7]

8. Rocha e Silva, M., and Graña, A.: To be published.

9. This material was supplied through the Brazilian Engine Factory Offices in New York.

Usually, three samples were simultaneously taken: one for estimation of histamine according to Code's method,[10] one for determination of leukocytes and platelets and one to check on the coagulability of the blood.

The experiments on perfusion of the liver were performed in the following way: In an anesthetized dog, a cannula with a drain was inserted into the carotid artery; the abdomen was opened and the hepatic artery clamped; after complete exsanguination through the carotid artery drain, a cannula was quickly inserted into the trunk of the portal vein and 500 cc. of warm isotonic solution of sodium chloride passed through the liver to remove all traces of blood; after ligation of the rami to the portal vein distal to the cannula, the left and central lobes of the liver were tied off and excised; finally, the rest of the organ was freed from its connections with the diaphragm and abdominal organs and carefully transferred to an appropriate heated funnel, while the perfusion with Tyrode solution or defibrinated blood started. The collected perfusates, flowing at a rate of 10 to 12 cc. per minute were tested every four to five minutes on a fragment of guinea pig ileum, sensitive to 0.02 microgram of histamine.

RESULTS

Experimental Perfusion of Liver with Ascaris Extracts, Horse Serum, Trypsin and Mercury Bichloride.—As shown in the preceding paper,[7] the injection of a potent ascaris extract into the veins of normal dogs produces an enormous engorgement of the liver, with stasis in the portal region and discharge of histamine into the general circulation. That this histamine which appears in large amounts in the circulating blood comes from the liver cells was definitely shown by the fact that there is a considerable decrease in total histamine extractable from pieces of liver taken after shock. On the other hand, the increases in blood histamine are usually much more conspicuous when the samples are taken directly from the portal vein. The analogy with what occurs in true anaphylactic shock is manifest. Ojers, Holmes and Dragstedt [6] have shown that liver histamine decreases after shock and that there is a close correspondence between this decrease and the gravity of shock. In the case of the shock produced by ascaris extracts, this proportionality was not verified in every instance, since in a small number of animals the shock was not accompanied with much discharge of histamine or heparin into the circulating blood, and yet the blood pressure fell rapidly to zero. But in most of the animals the liver histamine was reduced to one half or one third of the initial value. This would mean a release of milligrams of histamine from the total organ, or at least of many hundreds of milligrams of histamine base from pieces of liver weighing 100 to 200 Gm. In order to ascertain whether this release of histamine was the consequence of a direct action of the ascaris extracts on liver cells or another mechanism was involved in the production of the phenomenon, we submitted the livers of 7 dogs to the perfusion

10. Code, C. F.: J. Physiol. **89**:257, 1937.

with Tyrode solution or defibrinated blood. Usually, only a half or a third of the total mass of the liver was submitted to perfusion. As a rule, after the experiment with the ascaris extract, the conditions of the perfusion were checked by injection of either crystalline trypsin or mercury bichloride. Chart 1 shows the results obtained in the per-

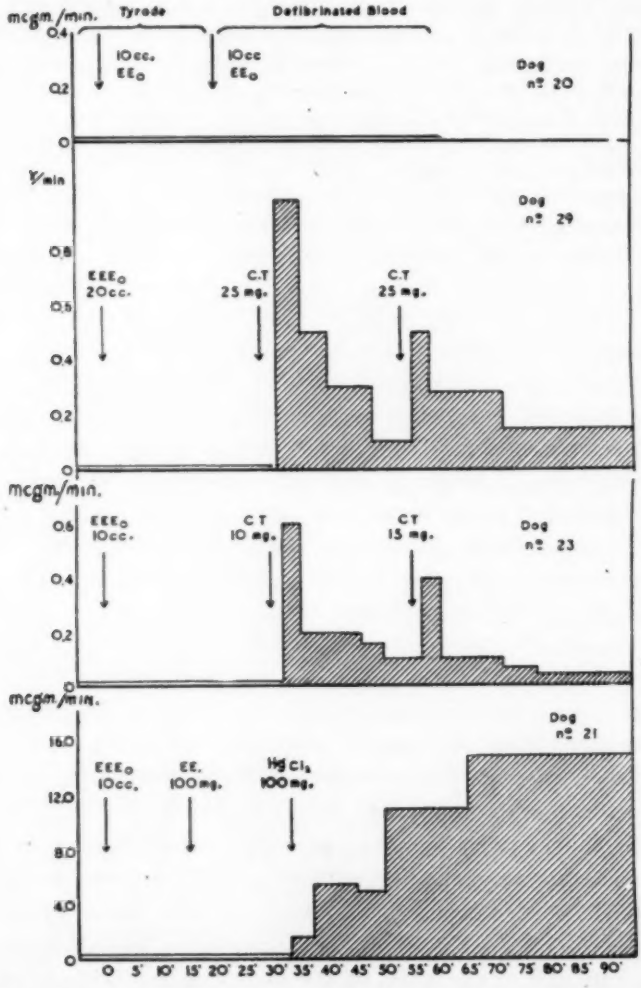

Chart 1.—The graphs show the course of experiments of liver perfusion performed in 4 dogs. As seen, the injection of 10 to 20 cc. of a potent ascaris material (EEE_0) or a highly purified material (EE_1) is unable to liberate histamine from liver cells. The injection of 10 to 25 mg. of crystalline trypsin or 100 mg. of mercury bichloride was regularly followed by a copious release of active free histamine. Dog 29 was hypersensitive to ascaris extract, by a previous injection of the material.

fusion of the livers of 4 dogs, 1 of which had been previously sensitized to ascaris extract by two subcutaneous injections of the material

twenty days before the experiment. It would be expected that this animal should be hypersensitive to the effects of ascaris extracts.

In most of the dogs the extract was injected directly into the cannula connected with the portal vein, but in some dogs it was injected far away from the cannula to permit a dilution of the extract and, consequently, a longer contact of it with the liver cells. In no case did ascaris extract produce any detectable release of histamine from isolated liver of dogs. It is interesting to recall that the fragment of guinea pig ileum used for assaying the perfusates was sensitive to hundredths of a microgram of histamine and that amounts at least one hundred thousand times greater would be expected to be released from the fragments of the liver submitted to the perfusion by calculating from in vivo experiments. To exclude the possibility that ascaris extracts might liberate an inactive compound of histamine with some cell constituents in several instances, the perfusates were submitted to Code's method of extraction with entirely negative results. Furthermore, pieces of the isolated liver were taken before and after the injection of ascaris extracts into the perfusing cannula and there was no indication of a decrease in the histamine which can be extracted from the organ. As the effect on the liver in the intact dog might depend on products derived from the abdominal organs, we perfused the whole mass of abdominal viscera of 1 dog. A cannula was tied into the trunk of the thoracic aorta and the perfusate collected from the inferior vena cava, just above the diaphragm. After washing out the blood, perfusion with Tyrode's solution was started, and 20 cc. of a very potent ascaris extract was injected into the arterial cannula. Even in this case, there was no release of detectable amounts of histamine.

Two of the animals used had been previously sensitized to horse serum. Before injecting the ascaris extract, 20 cc. of horse serum was injected into the portal cannula. No histamine appeared in the perfusates after thirty minutes of experiment.

From those experiments we can conclude that dogs' liver does not yield histamine by in vitro anaphylaxis or after the injection of an agent which produces severe anaphylaxis-like reaction in the intact dog. This means that the direct contact of the antigen with the sensitized liver cells is not enough to discharge the histamine. It is interesting to recall that in 1917 Weil [11] was unable to obtain any evidence of the release of an anticoagulant (heparin) following direct perfusion of the liver of sensitized dogs with Locke's solution plus antigen. Furthermore, all indications of a release of an anaphylatoxin from dogs' liver were given when sensitized liver was inserted into

11. Weil, R.: J. Immunol. **2**:525, 1917.

the circulation of a normal animal, as shown in the experiments of Manwaring and associates.[12] So far, there has been no indication in literature of a release of an active histamine-like substance from the isolated sensitized dogs' liver after the injection of the antigen.

The only effect so far observed in dogs' liver in experiments of perfusion with the antigen has been the moderate reduction of perfusion flow, as observed by Mautner and Pick.[13] In our experiments with ascaris extracts and horse serum, the decrease in the volume of perfusate in five minutes was slight but detectable. In 1 experiment, for instance, the volume of perfusate dropped from 83 cc. in five minutes to 65 cc. after the injection of 20 cc. of ascaris extract into the portal cannula. Five minutes later, however, the volume returned to 80 cc. A much more striking reduction in the perfusion flow was observed after the injection of trypsin. In 1 experiment, the volume of flow varied from 80 cc. in five minutes to 48 and 38 cc. and went up again to 60 cc. within twelve minutes after the injection of trypsin. A new injection of trypsin produced a new diminution of flow to 50 cc. in five minutes and a prompter return to normal.

Mechanical Shock.—Contrasting with the type of shock occurring in most of the animals given the ascaris extracts intravenously, there is a kind of shock produced by ascaris extract, with practically no changes in the histamine content or in the coagulability of the blood. This was clearly seen in dog 31. Although the blood pressure went down and the animal died thirty minutes after the injection of ascaris extract without showing any sign of recovery, the blood histamine was low in the normal range, and the coagulability of the blood was altered only in the later stages of the shock. All the morphologic characteristics of very severe shock were present. The liver was enormously engorged with blood and definitely dark or black; the turgescence in the portal vein was maximal, and yet there was no increase in the histamine content of either the femoral or the portal vein. The leukocytes went down from an initial value of 11,600 to 5,800 six minutes after the injection of 15 cc. of the crude ascaris extract. The samples of blood collected one, three, six and eight minutes after the injection of the ascaris extract clotted in two, fifteen, thirty and thirty minutes respectively. The samples collected seventeen to thirty minutes after injection of the ascaris extract did not clot in twenty-four hours, indicating a late release of an anticoagulant. The blood histamine, however, was low even in those samples which did not clot.

12. Manwaring, W. H.; Hosepian, V. M.; O'Neill, F. J., and Moy, H. B.: J. Immunol. **10**:575, 1925.

13. Mautner, H., and Pick, E. P.: Biochem. Ztschr. **127**:72, 1922.

This picture of severe shock, with only a moderate release of histamine and heparin, has been tentatively named "mechanical shock" and seems to be the commonest kind of shock observed with hydatid fluid, as shown in a previous paper.[8] In his studies on blood histamine in anaphylactic shock, Code [14] stated that in a few dogs the increases in blood histamine were not enough to explain death, since the animals died even after the blood histamine returned to normal. On the basis of the findings in a few animals into which ascaris extracts had been injected we are now inclined to assume that there is a component of the anaphylactic shock in dogs that strongly suggests a mechanical obstruction of the portal circulation without much release

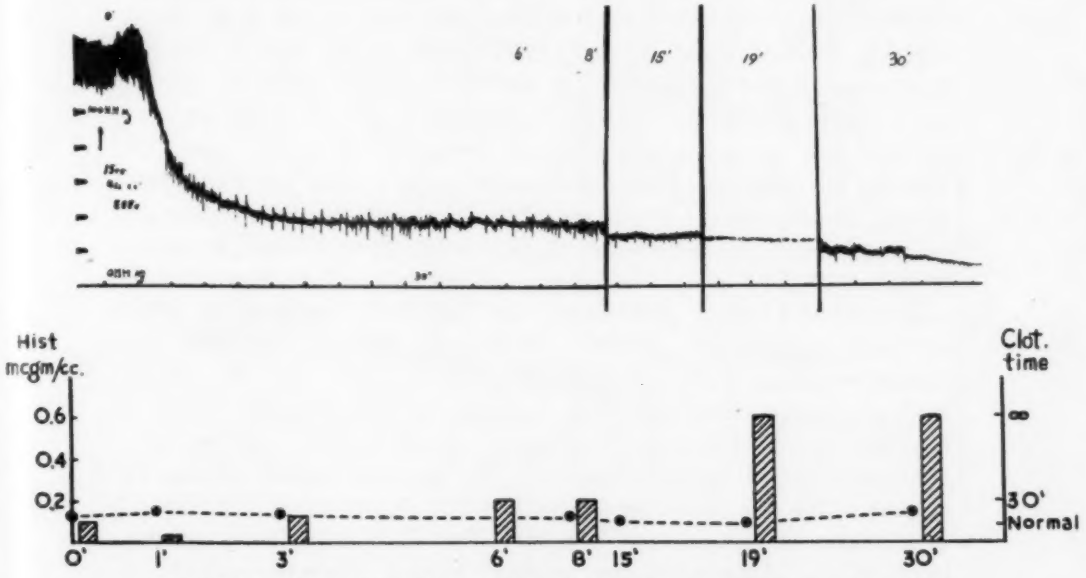

Chart 2 (dog 31).—After the injection of 15 cc. of a very potent ascaris extract, an extremely severe shock developed in the animal, without changes in the histamine of blood samples taken in the femoral and portal veins. The incoagulability of the blood became extreme only within nineteen minutes after the injection.

of active substances like histamine and heparin. We estimate that in 1 of 20 animals into which ascaris extracts are injected this sort of mechanical shock develops. It is logical to conclude, therefore, that even when there is a release of active substances the "mechanical" component is also present and that this anaphylaxis-like reaction produced by ascaris extract in dogs results from the superposition of those two kinds of shock, being only a question of degree if in 1 animal the "chemical" component is more pronounced than the

14. Code, C. F.: Am. J. Physiol. **127**:78, 1939.

"mechanical" one or vice versa. We have many reasons to believe that this dual mechanism might explain many details of true anaphylactic shock produced by the reinjection of horse serum in dogs.

On the probable mechanism of production of this obstruction in the circulation in the liver we can hypothesize that a clumping of leukocytes and platelets, as shown to occur in anaphylactic shock,[8] might be the working mechanism. For a reason not yet understood, there is no explosion of platelets and the chain of events leading to the liberation of histamine and heparin is broken somewhere and the process discontinued.

Inhibitory Effect of Glycogen on the Release of Histamine and Heparin During Shock.—As shown in the preceding material, ascaris is unable to liberate histamine from isolated dog liver perfused with Tyrode solution or defibrinated blood. This would induce one to conclude that some of the components of the blood are indispensible for the in vivo release of histamine from liver cells as shown in the preceding paper.[7] Our attention was primarily directed toward leukocytes and platelets as being the probable elements indispensable for the in vivo release of histamine from liver cells, since leukocytes and thrombopenia are inevitable occurrences during anaphylactic shock. It became necessary to find a suitable reagent to remove one or both of these elements from blood. Fortunately, we have been studying the effects of liver glycogen on rabbits' blood and observed that this substance practically removed platelets from circulating blood. Besides that, glycogen produces a sharp reduction in the leukocyte count, as observed first by Staub and associates [15] and later confirmed by us.[8]

Thus glycogen appeared to constitute the appropriate reagent for a study of the role played by the hematologic elements in the production of a release of histamine and heparin from liver cells during anaphylactic shock. Injected a few minutes before, glycogen partially or totally desensitized the animals to a subsequent injection of the ascaris extract. The fall of blood pressure in the carotid artery was definitely reduced (charts 3 and 4) and the shock which occurred never had the extreme severity of the shock usually produced by ascaris extract alone. In most of the cases, the fall of carotid blood pressure was reversible and recovery followed promptly. A second injection of the same extract was practically without effect. Moreover, the drop in blood pressure was not so sharp, and usually a slow decrease occurred without much impairment in the heart beat and respiratory movements. Contrasted with the enormous engorgement of the liver occurring in almost all animals given injections of ascaris extracts alone, the organ usually retained its red-brown appearance when 3 to 8 Gm. of liver glycogen was

15. Staub, H.; Mezey, K., and Golandas, G.: Klin. Wchnschr. **17**:1501, 1938.

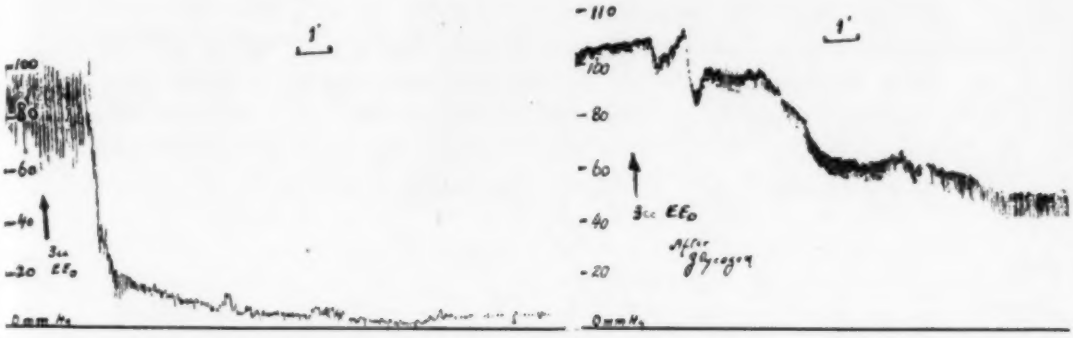

Chart 3 (dogs 41 and 40).—Modification of the intensity of the shock produced by ascaris extract following a previous injection of 8 Gm. of glycogen. At the left, ascaris extract was injected alone; at the right, the extract was injected a few minutes after the injection of glycogen. Femoral artery tracings.

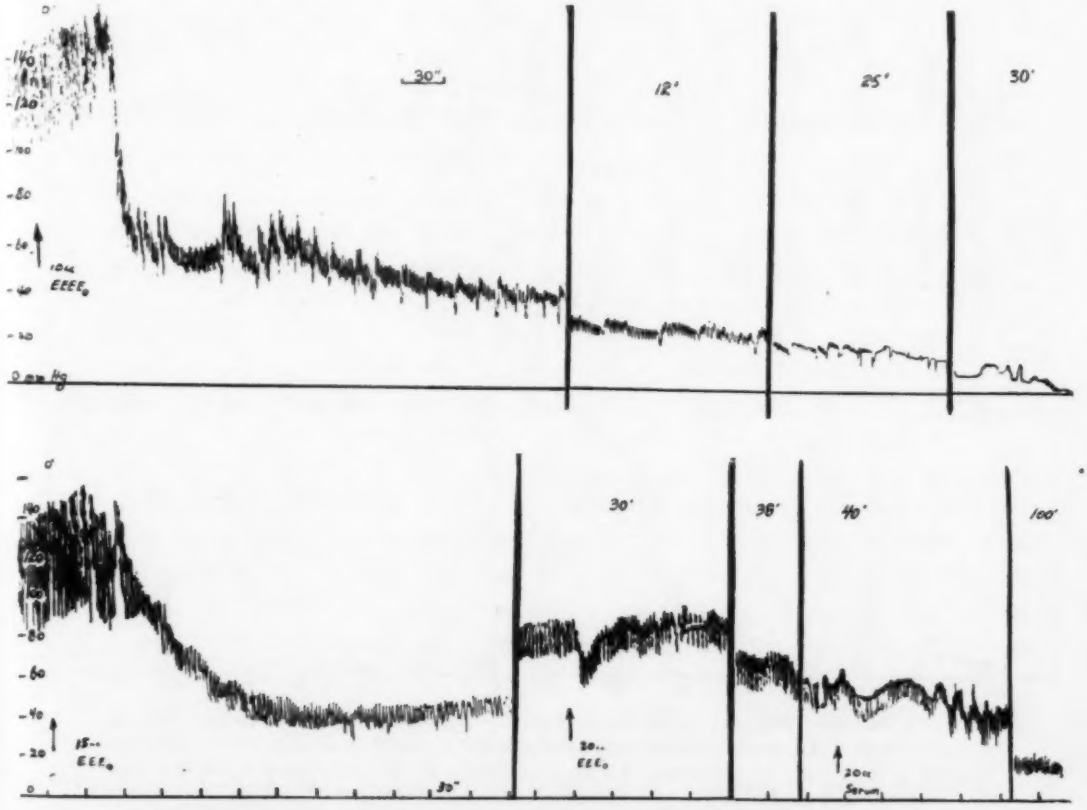

Chart 4.—Upper tracing: Dog 33 received 10 cc. of an ascaris extract; the blood histamine went up to a level of 1.5 microgram per 1 cc., and the incoagulability of the blood was extreme. Lower tracing: Dog 28 received 15 cc. of ascaris extract, five minutes after the injection of 6 Gm. of liver glycogen; the blood histamine went down, and the blood clotted normally. This animal was sensitized to horse serum. As seen, an injection of 20 cc. of horse serum did not influence blood pressure. The animal died in secondary shock one hundred minutes later.

injected before the ascaris extract. In a few animals, however, when greater volumes of ascaris material were injected a severer type of shock occurred, even when the animal was prepared by a previous injection of glycogen. The remarkable fact observed was that the blood histamine did not increase when the ascaris extract was injected after a suitable dose of glycogen. The incoagulability of the blood also

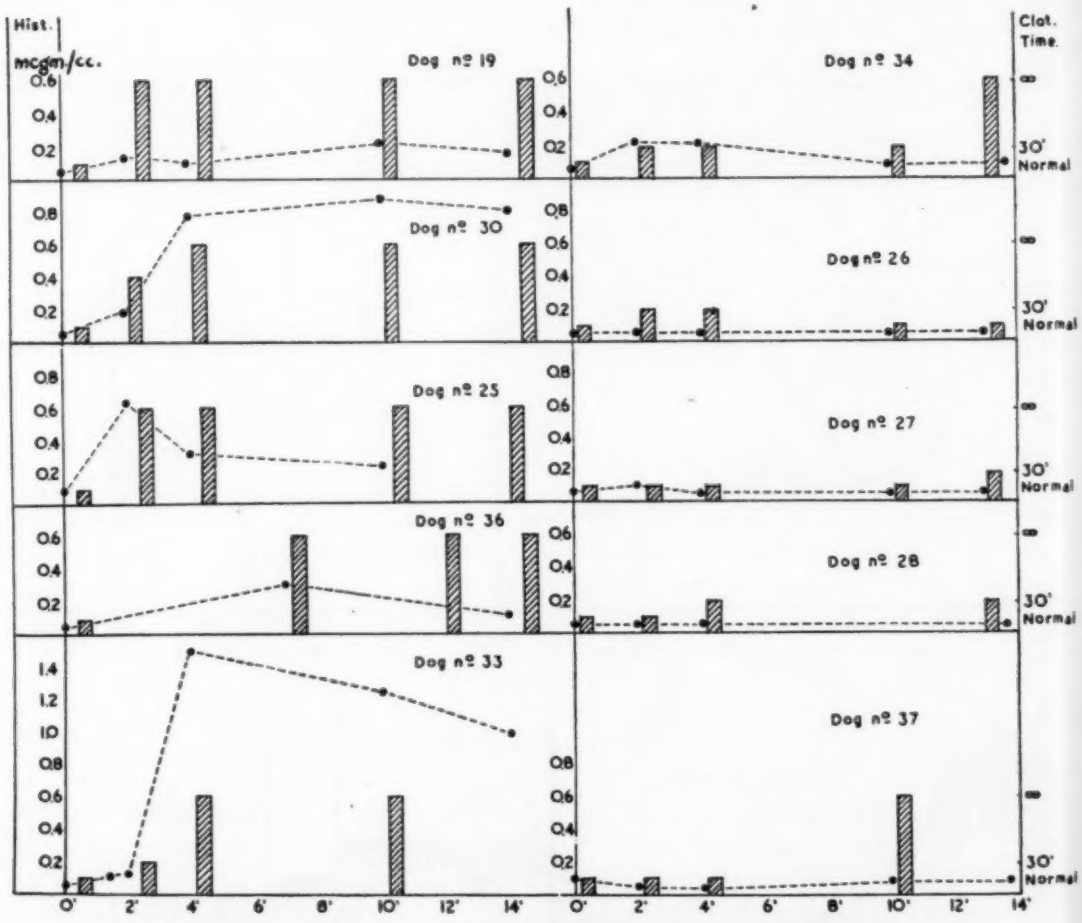

Chart 5.—Inhibitory effect of glycogen on the release of histamine and heparin in 5 dogs (at the right) which received ascaris extracts after a previous injection of 3 to 8 Gm. of glycogen. In the 5 animals at the left, ascaris extract was injected alone. Pointed lines represent blood histamine, and the rods, the degree of blood incoagulability.

was very slight, and only exceptionally did the blood become incoagulable. Even in the cases in which there was a significant fall of blood pressure, the blood histamine remained normal or below the norm

while the coagulability of the blood was altered very slightly. The graphs presented in chart 5 show the results of the experiments performed on 10 dogs, 5 of which (at the left) received ascaris extract alone while 5 others (at the right) received 3 to 8 Gm. of glycogen, two to five minutes before the extract was injected. It is apparent that glycogen almost entirely prevented the liberation of histamine or heparin.

In another sense this partial desensitization produced by glycogen might be of interest. It is generally agreed that desensitization to the antigen can be attained by means other than the immunologic exhaustion of antibodies (for a discussion of this point, see Dragstedt [16]). Peptone can desensitize dogs to a subsequent injection of the antigen. This might be partly due to a decrease of the mobilizable histamine of the liver, as suggested by Dragstedt, but we have now to consider that the desensitizing agent can also work on some of the components of the blood which are indispensable for the release of histamine and heparin from the liver cells. Glycogen appears to desensitize by dispersing platelets and leukocytes, and the same mechanism might hold true to explain unspecific desensitization to the antigen produced by several agents in sensitized animals.

Effects of Ascaris Extract and Glycogen on Leukocytes and Platelets.—In the preceding section it became clear that a previous injection of glycogen partially or totally removed from blood the component which is responsible for the release of histamine and heparin. This definitely reduced the severity of the shock, and in 2 dogs it entirely prevented the drop in systemic blood pressure. In a few dogs, however, the shock was moderately severe, especially when large amounts of ascaris extracts were injected, with a definite drop in blood pressure; but even in those dogs there was no change in the histamine content of the blood. This allows one to assume that glycogen entirely desensitizes the animal for the "chemical" type of shock while only partially desensitizing it for the "mechanical" type of shock. As glycogen produces a partial removal of leukocytes, as shown by Staub and associates,[15] and drastic reduction in the blood platelets, which fall almost to zero, as shown in the following material, one is warranted in concluding that the hematologic elements which are responsible for the release of histamine and heparin are the platelets, while the component responsible for the mechanical obstruction of capillaries and venules of the liver is the leukocytes plus platelets. This is further suggested by the results presented in the table, in which the leukocytes are recorded as estimated before and after the injection of glycogen and ascaris extract.

16. Dragstedt, C. A.: J. Immunol. **47**:1, 1943.

As can be seen, in many cases the drop in the leukocyte count was not extreme after the injection of glycogen. After the injection of the ascaris extract, a further decrease could be seen, and in some instances this decrease was very important.

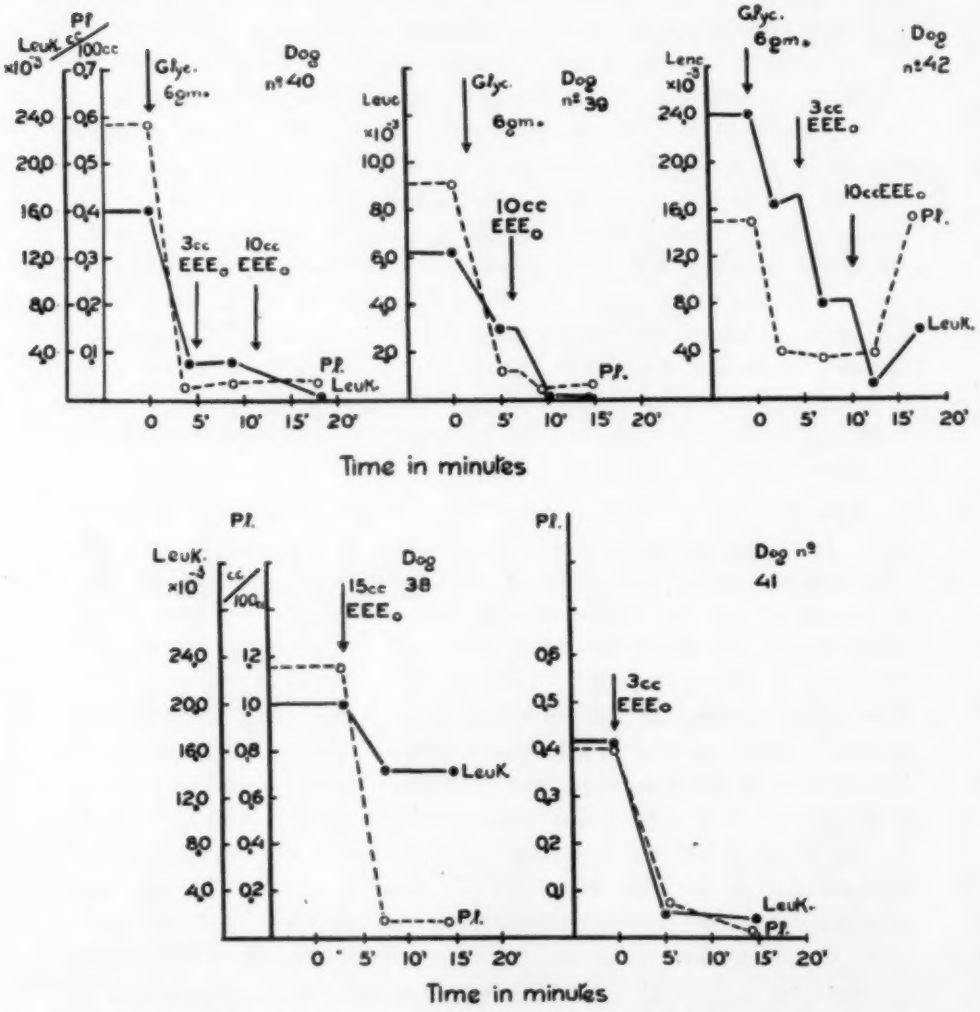

Chart 6.—Effects of glycogen and ascaris extracts on the leukocyte count and the platelet volume in 5 dogs. As seen, glycogen injected before ascaris extract almost completely removes platelets from circulating blood, in such a way that there is no further decrease following the injection of the ascaris extract.

In every case, however, the exclusion of blood platelets was complete after the injection of glycogen, as indicated by Fonio's method. In 5 animals, the volume of platelets was estimated by use of a Van Allen thrombocytocrit, and at the same time, leukocyte counts were made

by the usual method.[17] As shown in chart 6, reductions in platelet volume per hundred cubic centimeters of blood were extreme after injection of glycogen or Ascaris extract alone. If glycogen was injected before the ascaris extract there were no further variations in blood platelets after the injection of the ascaris extract. The leukocyte curves followed the same trend, but the decrease in leukocytes after the injection of glycogen was not so extreme as the reductions in platelets, leaving a margin for the ascaris extract to further remove those components of the blood.

Effect of Liver Glycogen and Ascaris Extracts on Total Leukocyte Counts

Dog	Weight, Kg.	Glycogen Injected, Gm.	White Blood Cells, Thousands			Intensity of Shock
			Before Injection	After Glycogen	After Ascaris Extract	
30	5.5	0	41.0	...	8.0	++++
31	20.0	0	11.6	...	5.8	++++
33	16.0	0	14.2	...	8.6	++++
35	16.5	0	20.1	...	2.4	++++
36	15.0	0	11.3	...	1.6	++++
38	5.7	0	19.6	...	14.0	+++
41	7.0	0	14.0	...	1.5	++++
26	9.5	3.0	13.6	2.6	0.2	++
28	14.0	6.0	14.6	6.4	2.0	+
27	15.0	6.0	7.6	3.8	3.4	++
37	17.0	8.0	12.4	8.3	1.9	+++
39	4.7	6.0	6.2	3.0	0	++
40	5.0	6.0	16.0	3.2	3.0	+
42	6.5	6.0	24.0	16.8	8.6	±

COMMENT

The interesting result obtained in the experiments of perfusion of dogs' liver with Tyrode solution or defibrinated blood was that the ascaris extract is unable to liberate histamine when put directly into contact with the liver cells. Similar experiments with negative results were performed in sensitized dogs by perfusing the liver with the antigen (horse serum). This negative result is a paramount factor for an understanding of the mechanism of the anaphylactic shock in this species of animal. There remains no doubt that the histamine which appears in vivo in the circulating blood derives from liver parenchyma, since there is a pronounced decrease in the histamine extractable from pieces of liver taken before and after shock. On the other hand, the histamine content in the portal vein increases quickly

17. Drs. W. O. Cruz and E. Martins, of the Oswaldo Cruz Institute, in Rio de Janeiro, Brazil, helped in the experiments with the Van Allen thrombocytocrit, which were performed in the hematologic laboratory of the Oswaldo Cruz Institute.

and attains levels which are much higher than those verified in the general circulation. This occurrence definitely indicates a powerful stagnation in the hepatic circulation, which can be directly perceived by the enormous increase in the volume of the liver during shock. To reconcile the negative findings of liver perfusion with the in vivo discharge of histamine and heparin from liver cells, one has to assume that some factor or factors existing in the intact blood are indispensable for the production of the anaphylactic shock. In a separate paper [8] we have shown that glycogen derived from ascaris extract, a polysaccharide substance extracted from hydatid fluid and glycogen extracted from dogs' liver produce in rabbits a definite leukopenia and thrombopenia, this accounting for the drastic reduction in blood histamine which occurs in those circumstances. Staub and associates [15] have made extensive studies on the leukopenia produced in dogs by macromolecular substances, like glycogen, starch and acacia, suggesting that the leukocytes which disappear from circulating blood will be retained in the capillaries of the lung and the skin. In our experiments, we have observed that glycogen also produces a thrombopenia but no changes in the arterial blood pressure. The leukopenia, however, is not so constant and depends on the anesthesia to which the animals have been submitted. When injected before the extract of ascaris, glycogen partially or totally desensitizes the dog against the ascaris material. Especially the incoagulability of the blood and the increase in blood histamine are powerfully reduced or inhibited when the injection of ascaris extract follows an injection of appropriate amounts of liver glycogen. This experiment can be properly interpreted by assuming that the previous injection of glycogen removes from blood some of the factors which contribute to the production of the shock. It is logical to conclude that glycogen exerts a dispersing effect on blood platelets in such a way that an accumulation of those hematologic elements in the liver never attains a concentration high enough to produce the explosive liberation of histamine and heparin in the case of their disintegration. Since ascaris extracts contain considerable amounts of a glycogen-like material, it seems probable that this substance has a great significance in aggravating the accumulation of platelets in the capillaries of the liver. We have to postulate, however, the interaction of an anaphylactic factor to localize in the liver the massive accumulation of blood platelets which otherwise would disperse all over the body. This factor might be the initial anaphylactic constriction of the hepatic veins, transforming the liver into a filter for the clumped elements of the blood. This initial constriction of the hepatic veins was seen in vitro by Mautner and Pick [18] in experiments of liver perfusion and definitely appeared in our experiments with ascaris extracts, horse serum and trypsin.

On the basis of this possibility, one might foresee the occurrence of a severe shock, without much liberation of histamine and heparin from liver cells. This kind of "mechanical" shock would be produced by the localization in the liver of the microthrombi of platelets and leukocytes. The actual occurrence of this kind of shock was definitely suggested by the experiment with dog 31, which was given intravenously 15 cc. of an extremely potent extract. The increase in blood histamine and the incoagulability of the blood were moderate, and yet the shock was extremely severe, with enormous engorgement of the liver and death in thirty minutes without any sign of recovery.

Finally, it seems indispensable to accept the interaction of another element from the blood or the liver cells to explain the discharge of histamine and heparin in the capillaries of the organ. It has been suggested by previous experiments that histamine is bound to cells forming a peptide bond which can be specifically ruptured by a tryptase ferment.[18] Furthermore, trypsin liberates active histamine and heparin, as shown before [19] and confirmed in the present report. The activation of proteases to explain the liberation of histamine in anaphylactic shock was suggested by Feldberg,[20] Rocha e Silva [21] and more recently by Dragstedt and Wells.[22] It seems logical to assume that activated plasma trypsin might be the agent responsible for the release of histamine and heparin. In this connection, it is interesting to recall that Iyengar [23] has observed that platelets contain a kinase which can activate trypsin by rupturing its connections with the trypsin inhibitor existing in the blood.

Thus the theory of the mechanism of anaphylactic shock in the dog which emerges from those experiments would postulate that the phenomenon develops in three stages: 1. There is an initial anaphylactic constriction of the hepatic vessels, effective in transforming the capillaries of the liver into a filter, which otherwise would be capillaries of the lung and the skin. 2. The leukocytes and platelets agglutinated in contact with the anaphylactic agent (antigen) will form microthrombi in the small vessels and capillaries of the liver. 3. After the latent period the platelets would "explode" liberating an enzyme factor which would act directly on the liver parenchyma, liberating the histamine and heparin which are discharged into the portal and general circula-

18. Rocha e Silva, M., and Andrade, S. O.: J. Biol. Chem. **149**:9, 1943.

19. Rocha e Silva, M.: Arch. f. exper. Path. u. Pharmakol. **194**:335, 1940.

20. Feldberg, W., and Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 671.

21. Rocha e Silva, M.: J. Pharmacol. & Exper. Therap. **77**:198, 1943.

22. Dragstedt, C. A., and Wells, J. A.: Quart. Bull., Northwestern Univ. M. School **18**:104, 1944.

23. Iyengar, N. K.: Indian J. M. Research **30**:467, 1942.

tion. The proteolytic nature of the enzymes which are activated after the rupture of platelets is suggested by the fact that histamine and heparin appear to be released from cells by the action of a ferment of the nature of a tryptase.

SUMMARY

Ascaris extracts, very active in producing an anaphylaxis-like reaction in the intact dog, are unable to produce a discharge of histamine from the isolated liver perfused with Tyrode solution or defibrinated blood. Similar negative results were obtained by perfusing sensitized dogs' liver with the antigen (horse serum). In identical circumstances, trypsin and mercury bichloride produced a discharge of conspicuous amounts of histamine.

A "mechanical" kind of shock in dogs following the injection of ascaris extracts is described. This type of shock, which is characterized by profound fall in blood pressure of the carotid artery but no increase in blood histamine or heparin, occurs in about 5 per cent of the animals given injections of ascaris extracts and apparently depends on a mechanical obstruction of the hepatic vessels by clumped leukocytes and platelets, without very much discharge of active substances.

Liver glycogen when given intravenously partially or totally desensitizes the animal toward the ascaris extract. Especially the discharge of histamine and heparin from liver cells can be entirely prevented by glycogen.

Liver glycogen almost entirely removes platelets from circulating blood and produces severe leukopenia. Those effects provided the explanation for the inhibitory effect produced by glycogen on the release of histamine and heparin from cells of the liver by ascaris extracts.

The implications of those facts for a better understanding of the mechanism of true anaphylactic shock are discussed.

STRUMA LYMPHOMATOSA

A Clinicopathologic Study

BERNARD J. FICARRA, M.D.
BROOKLYN

DISORDERS of the thyroid gland have fascinated surgeons since 1878, when Theodor Kocher first published his report of a successful thyroidectomy.[1] Accentuated interest in this subject found an impetus in 1912, when Hashimoto described a new pathologic entity in the thyroid gland.[2] Since he was the first to describe the lesion, it bears his name as well as the descriptive term "struma lymphomatosa."

This clinicopathologic entity is unusual because of its low incidence as well as its bizarre pathologic picture and symptom complex. A study of the literature unfolds many discrepancies as to the exact number of cases reported since it was first described by Hashimoto. In order to clarify this problem, Dr. A. Graham in 1931 studied the literature extensively.[3] He divided the reported cases into ten categories, interpreting and grouping them for statistical purposes. His analysis clearly demonstrated the existing confusion, duplication and lack of proper identification in the various cases reported. For this reason no accurate determination of the number of cases of struma lymphomatosa is possible. However, up to the present time, various authors have reported small series of cases.[4] Thus it can be appreciated that this

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From the Department of Surgery Kings County Hospital and Brooklyn Cancer Institute.

1. Kocher, T.: Exstirpation einer Struma retroesophagea, Cor.-Bl. f. schweiz. Aerzte **8**:702, 1878.

2. Hashimoto, H.: Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa), Arch. f. klin. Chir. **97**:219, 1912.

3. Graham, A.: Riedel's Struma in Contrast to Struma Lymphomatosa (Hashimoto), West. J. Surg. **39**:681 (Sept.) 1931.

4. (*a*) McClintock, J. C., and Wright, A. W.: Riedel's Struma and Struma Lymphomatosa (Hashimoto), Ann. Surg. **106**:11 (July) 1937. (*b*) McSwain, B., and Moore, S. W.: Struma Lymphomatosa, Surg., Gynec. & Obst. **76**:562 (May) 1943. (*c*) Joll, C. A.: Pathology, Diagnosis and Treatment of Hashimoto's Disease (Struma Lymphomatosa), Brit. J. Surg. **27**:351 (Oct.) 1939. (*d*) Kearns, J. E., Jr.: Struma Lymphomatosa, Ann. Surg. **112**:421 (Sept.) 1940. (*e*) Scarcello, N. S., and Goodale, R. H.: Struma Lymphomatosa, New England J. Med. **224**:60 (Jan. 9) 1941 (*f*) Jaffe, R. H.: Chronic Thyroiditis, J. A. M. A. **108**:105 (Jan. 9) 1937, (*g*) Clute, H.; Eckerson, E. B., and Wareen, S.: Clin-

(Footnote continued on next page)

entity is infrequently encountered during the professional career of the average surgeon.

By a comparison of the occurrence of struma lymphomatosa in a consecutive series of thyroidectomies, the rarity of this disease can be evaluated. With this objective in view, I have studied the number of thyroidectomies and the number of pathologically proved instances of Hashimoto's disease which have occurred in the hospitals in Brooklyn listed in table 1.

From the data available, it appears that only 5 cases of pathologically proved struma lymphomatosa were encountered over a period of five years at the hospitals listed in table 1. At one hospital (Jewish Hospital) the cases were reported as cases of thyroiditis and were not segregated according to types. However, from the present study it can be deduced that not more than 9 of these could be cases of struma

TABLE 1.—*Thyroidectomies and Struma Lymphomatosa in Various Hospitals in Brooklyn*

Hospital	Years Studied	Number of Thyroidectomies	Reported Cases of Struma Lymphomatosa
1. Brooklyn Hospital	1940 - 1944	215	1
2. Hospital of the Holy Family	1940 - 1944	160	3
3. Jewish Hospital	1940 - 1945	1,218	27 (reported as thyroiditis)
4. Kings County Hospital	1941 - 1945	345	1

lymphomatosa. During the same period, 1,938 thyroidectomies were performed. This statistical series definitely categorizes the disease among the rarities in surgery.

ETIOLOGY AND PATHOLOGY

The exact causation in the production of struma lymphomatosa is unknown. It has been suggested that exhaustive atrophy is a recognized change in Hashimoto's struma and that this degeneration might be associated with some form of compensatory hyperplasia resulting in this disease.[4a] Graham's study has led him to express the opinion that there is no proof that hyperthyroidism, hypothyroidism, suppuration, tuberculosis, syphilis or neoplasm are factors in the causation. Although the exact nature of the condition has not been determined, the current belief is that Hashimoto's disease should not be included in the same category with Riedel's struma.[3] Although frequently confused with Riedel's struma, many authors have concurred in the opinion that

ical Aspects of Struma Lymphomatosa, Arch. Surg. **31**:419 (Sept.) 1935. (*h*) Schilling, J. A.: Struma Lymphomatosa, Struma Fibrosa and Thyroiditis, Surg., Gynec., & Obst. **81**:533 (Nov.) 1945.

Riedel's struma and Hashimoto's disease are two distinct pathologic entities.[4g]

Micropathologic study of this disease reveals a dense, diffuse, lymphoid infiltration between the follicles, with occasional formation of secondary nodules. Sometimes these follicles are extremely prominent, so that the microscopic picture may closely simulate a lymph node. Hence the terminology struma lymphomatosa or, as it is sometimes called, lymphomatoid goiter.[4h] There tends to be a variation in the intensity of the lymphocytic infiltration, from occasional scattered lymphocytes among colloid-containing follicles or even absence of infiltration in certain areas to complete displacement of the normal thyroid, with confluent masses of lymphocytes forming secondary nodules. Other types of cells found are monocytes and occasionally plasmocytes. Notwithstanding the abundance of lymphocytic infiltration, the lymphoid tissue does not demonstrate a tendency toward definite formation of lymph nodes. That is, there is no formation of struma or sinuses.[4g]

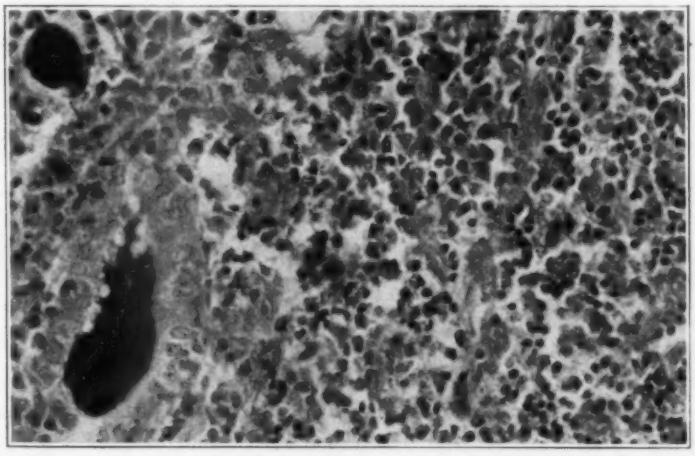

Fig. 1—Photomicrograph illustrating lymphocytic infiltration, with resulting distortion of the normal architecture of the thyroid gland, typifying struma lymphomatosa.

The connective tissue is usually swollen and poorly stained, and the cells have few nuclei. Mononuclear lymphocytes may be readily identified in the connective tissue. In rare instances, the interlobular and intralobular connective tissue may be sufficiently increased to predominate over the lymphocytic infiltrations. When this occurs, small islands of follicles are enclosed in the connective tissue.[5] It is areas of this

5. Boyd, W.: Surgical Pathology, Philadelphia, W. B. Saunders Company, 1943.

type which often lead to the erroneous belief that Hashimoto's disease is an early stage of Riedel's struma. Microscopic study of the blood vessels reveals no remarkable alteration in their normal architecture except for the fact that an abundance of round cell infiltration is noted around the larger vessels.

Thus struma lymphomatosa is a lymphoid goiter characterized by a growth of lymphatic elements in the formation of lymphoid follicles together with certain changes both in the parenchyma and in the interstitial tissues of the thyroid gland.

CLINICAL PICTURE

The disease occurs almost always in women. It has an insidious onset and follows a chronic course. The duration of symptoms may vary from nine months to five years or more. The clinical manifestations result from pressure of the hardened gland on the trachea. Usually there are no symptoms of a disturbed thyroid function in patients having the disease for a long period. When the disease is of a chronic nature, there is almost always an associated hypothyroidism at one time or another. The basal metabolic rate is usually within normal limits. On occasion, the basal metabolism may be below normal. Infrequently, evidence of mild myxedema may be noted.

A classical clinical history of struma lymphomatosa may be given as follows: The patient is a 40 year old woman who for many years' has had enlargement of the thyroid, which has grown rather slowly. She complains of weakness, fatigability, slight nervousness and some pressure symptoms. These pressure symptoms may be described as hoarseness, choking or dysphagia. On occasion a brassy cough or a roughening of the voice may be noted. The most satisfactory description of the gland in Hashimoto's disease has been provided by Dr. Richard B. Cattell, of the Lahey clinic. In order to palpate the gland adequately, the examiner should stand in front of the patient and turn the patient's head to the side to be examined. This will relax the sternocleidomastoid muscle. The examiner uses one hand to push the larynx toward the side to be examined. With the other hand, the thumb is pressed anterior to the sternocleidomastoid muscle and the second and third fingers are placed posterior to this muscle. The patient is then instructed to swallow. In so doing, the gland may be adequately palpated. In this way the length and breadth of the thyroid shield, the isthmus and the superior and inferior poles can be examined. The shape, size and consistency of the gland can thus be evaluated. When the lower pole is not felt, a roentgenogram of the trachea is indicated in order to determine tracheal deviation, substernal and subclavicular extension. The gland with Hashimoto's disease, when examined according to Dr. Cattell's method, will unfold the following diagnostic criteria:

1. The gland has a diffuse pebbly feel. 2. It feels as hard as exophthalmic goiter with involution of iodine. 3. The superior poles are extremely broad, being broader than the poles of primary hyperthyroidism. 4. The pyramidal lobe is enlarged similar to the enlargement of the lobe in primary hyperthyroidism.

By seeking to determine the presence of these criteria, one can make the preoperative diagnosis of struma lymphomatosa with greater accuracy.

DIAGNOSIS

The most valuable clinical aids in arriving at a diagnosis of struma lymphomatosa are to obtain an adequate history and to perform a satisfactory examination of the thyroid gland. If the signs and symptoms parallel the clinical picture previously presented, a tentative diagnosis of struma lymphomatosa can be made.

Struma lymphomatosa must be differentiated especially from other chronic infections and neoplasms of the thyroid gland. The most confusing lesions are:

1. Chronic nonspecific thyroiditis.
2. Chronic specific thyroiditis.
   (*a*) Tuberculosis.
   (*b*) Syphilis.
   (*c*) Actinomycosis.
3. Calcified adenomatous goiter.
4. Lymphosarcoma.
5. Carcinoma.
6. Riedel's struma.

Nonspecific thyroiditis is eliminated, since Hashimoto's disease displays the absence of inflammatory symptoms. Hashimoto's disease is bilateral, may be associated with hypothyroidism and does not have a tendency toward spontaneous cure. Specific granulomatous lesions are differentiated by the absence of any specific evidence of the causative organisms of tuberculosis, syphilis or actinomycosis. The enlargement of the thyroid gland in specific infections usually produces a soft gland and does not possess the other physical characters of struma lymphomatosa. Calcified adenomas, either solitary or multiple, are readily identified by calcific roentgenographic evidence of this type of degeneration.

Struma lymphomatosa may be difficult to differentiate from neoplastic lesions. However, it may be distinguished from malignant disease by the following points: 1. In struma lymphomatosa all areas of the gland are involved, without serious encroachment on tissue outside the thyroid gland. 2. Neoplasm involves all areas, including the main vessels and nerves. 3. Struma lymphomatosa does not produce an irregular nodular

surface of the gland. 4. Regional glandular enlargement due to metastases is absent in struma lymphomatosa and is usually prominent in neoplasms.

Whenever a satisfactory differentiation between carcinoma of the thyroid and struma lymphomatosa is not possible, pathologic study of the operative specimen will decide the question.

The present tendency among pathologists and surgeons is to regard struma lymphomatosa and Riedel's struma as distinct diseases.[6] Often these entities are difficult to differentiate from each other. For this reason, table 2 is significantly valuable.

In addition to the points given in table 2, Riedel's struma may be "frozen" in the neck. It is the hardest pathologic entity (except a calcified adenoma) felt in the neck. It is hard as cartilage and cuts with difficulty. Hence it has been called "iron struma" or "ligneous" or "woody thyroiditis."

TABLE 2.—*Differentiation of Hashimoto's Disease and Riedel's Struma*

	Hashimoto's Disease	Riedel's Struma
1.	It is practically always confined to women	Disease is reported equally in men and women
2.	A history of myxedema may be obtained	There is little tendency toward myxedema, especially following operation
3.	Glandular involvement is diffuse and bilateral	Involvement is usually unilateral, following a discrete nodule
4.	Pressure symptoms are infrequent	Pressure symptoms, such as hoarseness, difficulty in swallowing and limitation of the cord on the involved side, are common
5.	Periglandular adhesions are absent	Pronounced adhesions to adjacent structures are found
6.	Pyramidal lobe is prominent	Pyramidal lobe is usually not prominent
7.	Histologically fibrosis is circumscribed	Histologically fibrosis is diffuse
8.	Lymphoid hyperplasia is pronounced	There is no lymphoid hyperplasia
9.	There are no Dorothy Reed cells	Dorothy Reed cells can be identified

TREATMENT

Operation in struma lymphomatosa is indicated for two reasons: (1) to differentiate the lesion from cancer and (2) to relieve or prevent pressure symptoms. At the time of operation the true identity of the pathologic change in the thyroid is revealed. The gland with Hashimoto's disease is enlarged from two to five times the normal size. It is not adherent to adjacent structures. Thus it is immediately differentiated from cancer or Riedel's struma. The gland is gray-pink and is firm. When sectioned, it is white, with a suggestion of focal edema. Compression of the gland with a clamp results in the extrusion of a serous fluid. Clamps grasp the tissue poorly and hold fast only to the fibrous capsule and to the blood vessels in the gland parenchyma.

6. McClintock and Wright.[4a] Clute, Eckerson and Wareen.[4g] Schilling.[4h]

Bleeding is not remarkable, because of compression and at times complete occlusion of blood vessels. This occlusion results from an increased fibrofollicular pressure, which is characteristic of Hashimoto's disease.

The surgical procedure is a routine subtotal thyroidectomy. However, the operation is less radical than that for primary hyperthyroidism. The remnants of the thyroid are sutured to the trachea in such a way that the midline of the trachea is free of thyroid tissue. By the prevention of contiguity of the remnants of the thyroid the possibility of future tracheal compression is avoided.

The postoperative course is usually uncomplicated. Brawny thickening of the cutaneous layers may occur, and it may persist for many weeks. In most instances myxedema can be anticipated. Patients should be advised of this possibility prior to operation. For this reason patients are followed postoperatively with routine determinations of the basal metabolic rate and the cholesterol level. Control of the myxedema is not difficult with a daily dose of thyroid extract. After operation these patients are much relieved, and they are perfectly well as soon as the myxedema is controlled. There have been no reported instances of recurrence of the disease following thyroidectomy. Operative mortality does not differ from the mortality in routine subtotal thyroidectomies.

PROGNOSIS

Untreated struma lymphomatosa may pass into myxedema. After thyroidectomy, complete and permanent relief of pressure symptoms results, although the onset of hypothyroidism may be accelerated. If this condition is anticipated, the postoperative administration of thyroid extract should be commenced as soon as incipient myxedema is suspected.

Postoperative recurrence is not usual. So-called recurrence can be attributed to inadequate surgical treatment. This occurs if the bilateral nature of the disease is not recognized and results in a unilateral resection which fails to relieve adequately the pressure symptoms. "It is a mistake to assume that the disease has in the interval merely spread from one lateral lobe to the other, for which view there is no reliable evidence. The explanation is most probably that in certain asymmetrical goiters (based on congenital asymmetry of the thyroid gland) one large lateral lobe may so overshadow the other small lobe that the latter is allowed to remain undisturbed." [4c]

SUMMARY AND CONCLUSION

Previous literary studies have indicated that Hashimoto's disease is listed among the rarer surgical entities. Our present study has corroborated this belief. Over a five year period, only 5 pathologically verified cases of struma lymphomatosa have been encountered in the

hospitals surveyed. At one hospital the cases were reported as thyroiditis. During this same period, 1,938 thyroidectomies were performed.

The salient feature of this disease is that its exact causation is unknown. It occurs almost entirely in women in the third, fourth and fifth decades of life. The fundamental pathologic change is a lymphocytic infiltration associated with follicular pressure atrophy. Vascular channels are obstructed because of fibrofollicular pressure. Clinically the most important findings are demonstrated by palpation of the thyroid gland. The features of struma lymphomatosa are broadening and enlargement of the superior poles and hard, firm lobes, giving the impression of a pebbly surface. Enlargement of the pyramidal lobe, as in hyperthyroidism, is notable. Pressure symptoms may or may not be present. Surgical treatment is indicated to relieve pressure symptoms and to differentiate the disease from neoplasm.

Little knowledge is present as to the course of untreated Hashimoto's disease, since patients in all the reported cases have been subjected to operation or radiation therapy. Thyroidectomy will relieve pressure and nervous symptoms. If postoperative myxedema occurs, it can be counteracted by the administration of thyroid extract.

CORRECTION

In the article by Dr. A. de Sousa Pereira entitled "A Basis for Sympathectomy for Cancer of the Cervix Uteri," in the March issue (ARCH. SURG. **52**:260, 1946), the drawings in the upper right hand corner of figure 4 (page 267) and of figure 8 (page 271) are transposed.

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